Title: A Double Blind, Randomized, Placebo Controlled, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy on LDL-C of Evolocumab (AMG 145) in Subjects With HIV and With Hyperlipidemia and/or Mixed Dyslipidemia

Amgen Protocol Number (AMG 145/Evolocumab) 20130286

BEIJERINCK: evolocumaB Effect on LDL-C lowerIng in subJECts with human immunodeficiency viRus and INcreased Cardiovascular risK

EudraCT number 2015-004735-12

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Date: 19 November 2015

Amendment 1: **30 January 2017**

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NCT Number: NCT02833844
This NCT number has been applied to the document for purposes of posting on clinicaltrials.gov

Investigator's Agreement

I have read the attached protocol entitled A Double Blind, Randomized, Placebo Controlled, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy on LDL-C of Evolocumab (AMG 145) in Subjects with HIV and with Hyperlipidemia and/or Mixed Dyslipidemia, dated **30 January 2017**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to one year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

Protocol Synopsis

Title: A Double Blind, Randomized, Placebo Controlled, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy on LDL-C of Evolocumab (AMG 145) in Subjects with HIV and with Hyperlipidemia and/or Mixed Dyslipidemia

Study Phase: 3b

Indication: Hypercholesterolemia and/or mixed dyslipidemia

Primary Objective: To evaluate the effect of 24 weeks of subcutaneous (SC) evolocumab administered every month (QM) compared with placebo QM on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in human immunodeficiency virus (HIV)-positive subjects with hyperlipidemia or mixed dyslipidemia.

Secondary Objectives:

- To assess the effects of 24 weeks of SC evolocumab QM compared with placebo QM on change from baseline in LDL-C, and percent change from baseline in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol (TC), lipoprotein(a) [Lp(a)], triglycerides, HDL-C, and very low-density lipoprotein cholesterol (VLDL-C), in HIV-positive subjects with hyperlipidemia or mixed dyslipidemia
- To assess the effects of 24 weeks of SC evolocumab QM compared with placebo QM on percent of subjects attaining LDL-C < 70 mg/dL (1.8 mmol/L) in HIV-positive subjects with hyperlipidemia or mixed dyslipidemia
- To assess the effects of 24 weeks of SC evolocumab QM compared with placebo QM on percent of subjects attaining a 50% reduction in LDL-C from baseline in HIV-positive subjects with hyperlipidemia or mixed dyslipidemia

Safety Objective: To evaluate the safety and tolerability of SC evolocumab QM compared with placebo QM in HIV-positive subjects with hyperlipidemia or mixed dyslipidemia

Hypotheses: Subcutaneous evolocumab QM will be well tolerated and will result in greater reduction of LDL-C, defined as percent change from baseline at week 24 compared with placebo QM in HIV-positive subjects with hyperlipidemia or mixed dyslipidemia.

Primary Endpoint: Percent change from baseline in LDL-C at week 24

Secondary Endpoints:

For week 24 the following secondary endpoints will be characterized:

- Tier 1
  - Change from baseline in LDL-C
  - Percent change from baseline in non-HDL-C
  - Percent change from baseline in ApoB
  - Percent change from baseline in TC
  - Achievement of target LDL-C < 70 mg/dL (1.8 mmol/L)
  - LDL-C response (50% reduction of LDL-C from baseline)
- Tier 2
  - Percent change from baseline in Lp(a)
  - Percent change from baseline in triglycerides
  - Percent change from baseline in HDL-C
  - Percent change from baseline in VLDL-C

Safety Endpoint(s):

- Subject incidence of treatment emergent adverse events
- Safety laboratory values and vital signs at each scheduled assessment
- Incidence of anti-evolocumab antibody (binding and neutralizing) formation

Study Design: This is a phase 3b, multicenter, double-blind, randomized, placebo-controlled study designed to assess the efficacy and safety of evolocumab in HIV-positive subjects with hyperlipidemia and/or mixed dyslipidemia.

Sample Size: Approximately 450 subjects will be enrolled in the study, with approximately 300 subjects in the evolocumab group.

Summary of Subject Eligibility Criteria: The study will enroll adult subjects (≥ 18 years of age) with known HIV infection, **who have received stable HIV therapy for ≥ 6 months prior to randomization and that is not expected to change during the duration of study participation. Subjects must be on stable doses of lipid-lowering therapy for ≥ 4 weeks and not expected to change during the duration of the study. Subjects should be on maximally tolerated dose of statins. For some subjects, "maximally tolerated" may indicate no statin at all due to statin intolerance or contraindication to statin therapy. A statin-intolerant subject must meet the criteria described in Section 4.1.1, criterion 106. Subjects without known clinical atherosclerotic cardiovascular disease (ASCVD) must have fasting LDL-C of ≥ 100 mg/dL (2.6 mmol/L) or non-HDL-C of ≥ 130 mg/dL (3.4 mmol/L) as determined by the central laboratory at screening. Subjects with known clinical ASCVD must have fasting LDL-C of ≥ 70 mg/dL (1.8 mmol/L) or non-HDL-C of ≥ 100 mg/dL (2.6 mmol/L) as determined by the central laboratory. Clinical ASCVD is defined as a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin. Subjects must also have fasting triglycerides ≤ 600 mg/dL (6.8 mmol/L).**

For a full list of eligibility criteria, please refer to Section 4.1 through Section 4.1.2.

Investigational Product: Evolocumab or matching placebo administered by automated mini-doser (AMD) or prefilled autoinjector (AI)/Pen.

Amgen Investigational Product Dosage and Administration:

The Amgen investigational medicinal product (IMP) is evolocumab and placebo. The Amgen investigational product (IP) is the IMP plus the device (AMD **[called an "on-body infuser prefilled cartridge" in the United States** or AI/pen). In this document, IMP will be referred to as IP.

Double-blind Treatment Period:

Evolocumab 420 mg or matching placebo will be administered QM at day 1 and weeks 4, 8, 12, 16, and 20 as an SC injection. The IP **ma**y be delivered by AMD **or by** 3 injections with AI/pen. Observed, in-clinic dosing should occur at day 1 and week 20.

Open-label Period:

Subjects who receive a dose of IP at week 20 will continue in an open-label period where all subjects will be treated with evolocumab 420 mg QM at weeks 24, 28, 32, 36, 40, 44, and 48. Dosing at week 24 is expected to be in-clinic while the remaining doses will be at an appropriate non-clinic setting (eg, at the subject's home). Subjects who do not wish to self-inject in a non-clinic setting (eg, at the subject's home) may return to clinic for injection.

Procedures:

After subjects complete the informed consent form, screening should be completed and the subject randomized or screen failed after 4 weeks (± 1 week) of signing the informed consent. Subjects will undergo SC placebo injection with **the** device **anticipated** to be used during study **(**AMD or AI/pen**)** during screening. Subjects who tolerate the placebo injection, complete all screening procedures, and successfully meet all eligibility criteria at the end of screening will enter the double-blind treatment period.

Subjects will be randomized via interactive voice response system/interactive web response system (IVRS/IWRS) and will return to the study site for day 1 procedures while continuing their background HIV and lipid-lowering (if applicable) treatment. Baseline evaluations will be performed on day 1 of treatment before subjects receive the first dose of IP. Laboratory tests will be conducted at day 1 and week 12. Vital signs, safety data reporting, **urine pregnancy testing**

(as applicable), and concomitant therapy will be recorded at each visit. At the end of the double-blind treatment period at week 24, laboratory tests will be conducted, and vital signs, safety data reporting, **urine pregnancy testing (as applicable)** concomitant therapy, physical examination, and body weight/waist circumference will be recorded.

Following the double-blind treatment period, subjects who received a dose of IP at week 20 will continue to a **24**-week open-label period in which all subjects will be treated with QM evolocumab at weeks **24,** 28, 32, 36, 40, 44, and 48. Laboratory tests will be conducted at week 36 and week 52 . Vital signs, safety data reporting, **urine pregnancy testing (as applicable),** and concomitant therapy will be recorded at week 36. At end of study week 52, vital signs, safety data reporting, **urine pregnancy testing (as applicable),** concomitant therapy, physical examination, body weight, and waist circumference will be recorded.

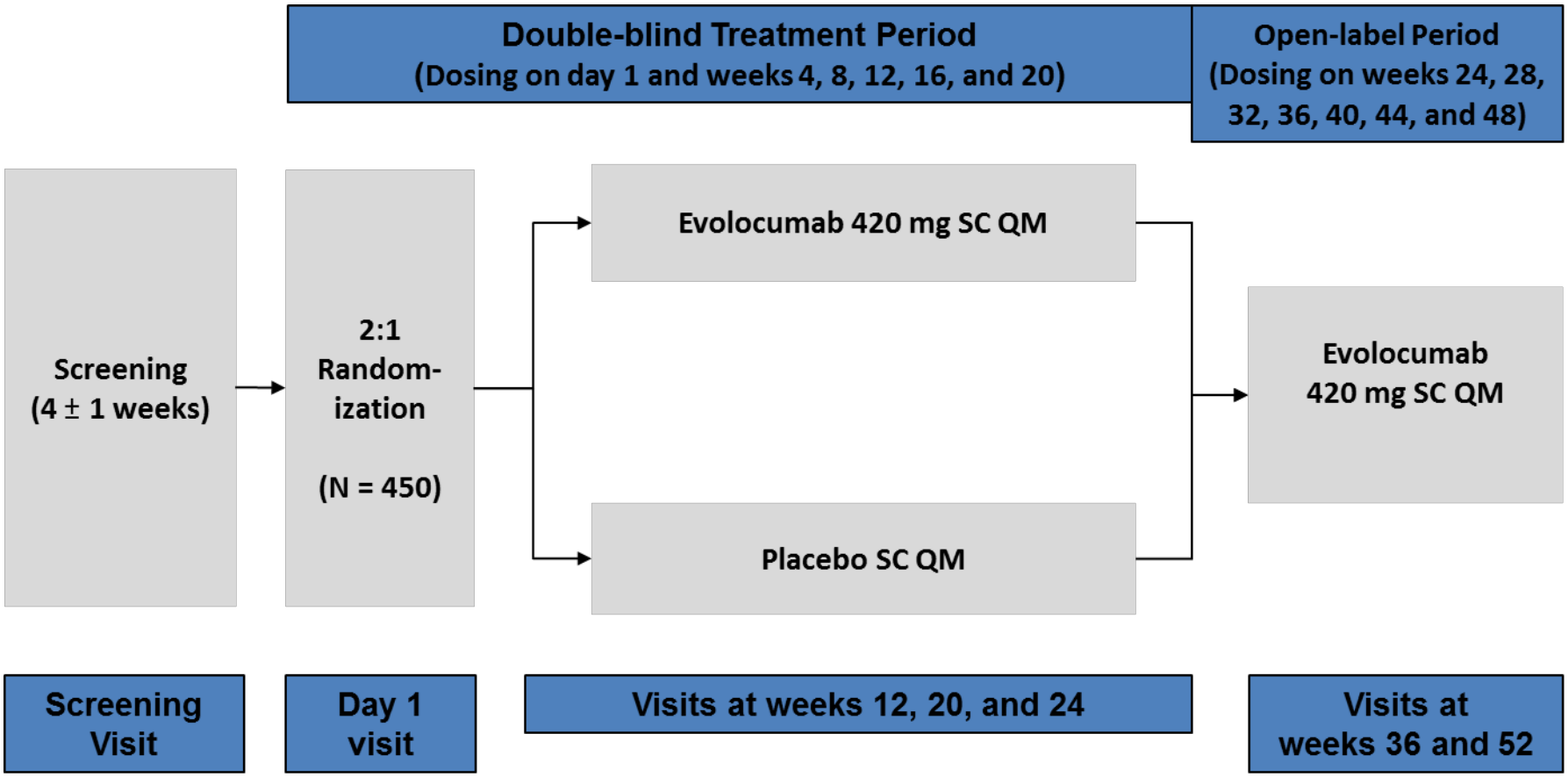
The overall study design is described by a study schema at the end of this synopsis section. For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 3).

Statistical Considerations: The primary analysis will be performed when all randomized subjects in double-blind treatment period have either completed all the scheduled study visits in the double-blind treatment period or have early terminated from the study. The superiority of evolocumab to placebo will be assessed for all efficacy endpoints on the full analysis set (FAS), which includes all randomized subjects who receive at least 1 dose of IP in the double-blind treatment period. To assess the primary endpoint of the mean percent change from baseline in LDL-C at week 24, a repeated measures linear effects model will be used on the FAS to compare the efficacy of evolocumab with placebo. The repeated measures model will include terms for treatment group, stratification factors, scheduled visit and the interaction of treatment with scheduled visit. Missing values will not be imputed for primary analysis. To evaluate the robustness of the analysis results, sensitivity analyses will be performed as follows: the primary analysis will be repeated using the computer analysis set (CAS); non-parametric analyses will be performed; a sensitivity analysis under the assumption that subjects who discontinued IP with missing endpoint data have a mean zero percent change from baseline will be conducted. The statistical model and testing of the tier 1 secondary efficacy endpoints will be similar to the primary analysis of primary endpoint. Analysis of the tier 2 secondary efficacy endpoints will use the same analysis model as the tier 1 endpoints. Safety endpoints will be summarized descriptively by treatment group.

Sponsor: Amgen Inc.

Data Element Standards Version(s)/Date(s):	Version 5/20 March 2015

Study Design and Treatment Schema



QM=once monthly; SC=subcutaneous

Study Glossary

Abbreviation or Term	Definition/Explanation
ASCVD	atherosclerotic cardiovascular disease
ADE	adverse device effect
AI	Autoinjector
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ApoA1	apolipoprotein A-I
ApoB	apolipoprotein B
AMD	automated mini-doser **(known as "on-body infuser prefilled cartridge" in the United States)**
AST	aspartate aminotransferase
BID	twice daily
CAS	computer analysis set
CD	cluster of differentiation 4
[redacted]	
CK	creatinine kinase
CPK	creatinine phosphokinase
CMV	cytomegalovirus
CRF	case report form
CTCAE	common terminology criteria for adverse events
CVD	cardiovascular disease
CYP	cytochrome P450
D-dimer	fibrin degradation product consisting of 2 crosslinked D fragments of fibrin
DILI	drug induced liver injury
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
End of Study (end of trial)	the date when the last subject has completed the assessments for week 52
End of Study (primary completion)	the date when the last subject has completed the assessments for week 24
End of Study for Individual Subject	the last day that protocol-specified procedures are conducted for an individual subject or the day the subject withdraws from study early

Abbreviation or Term	Definition/Explanation
End of Treatment	the day a subject receives the last treatment with investigational product before the subject completes the study or ends the treatment early
EOS	end of study
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
HDL-C	high-density lipoprotein cholesterol
HCV	hepatitis C virus
HIV	human immunodeficiency virus
hsCRP	high sensitivity C-reactive protein
ICF	informed consent form
ICH	International Conference on Harmonisation
IFU	Information for Use
IL-6	Interleukin-6
IL-10	Interleukin-10
IMP	investigational medicinal product
INR	international normalized ratio
IP	Investigational product
IPIM	Investigational Product Instruction Manual
IRB/IEC	institutional review board/independent ethics committee
IVRS	interactive voice response system, elecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
IWRS	interactive web response system
LAS	long-term analysis set
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
LH	luteinizing hormone
Lp(a)	lipoprotein(a)
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MI	myocardial infarction
PCSK9	proprotein convertase subtilisin/kexin type 9

Abbreviation or Term	Definition/Explanation
PI	protease inhibitor
PT	prothrombin time
QM	once monthly
RBC	red blood cells
RDW	red blood cell distribution width
SC	subcutaneous
sCD14	soluble cell differentiation antigen 14
[redacted]	
SD	standard deviation
SMART	Strategies for Management of Antiretroviral Therapy
Source Data	Information from an original record or certified copy of the original record containing patient IFU in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline E6). Examples of source data include Subject identification, Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
TBL	total bilirubin
TC	total cholesterol
ULN	upper limit of normal
VLDL-C	very low-density lipoprotein cholesterol
WBC	white blood cells

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1. OBJECTIVES

1.1 Primary

- To evaluate the effect of 24 weeks of subcutaneous (SC) evolocumab administered every month (QM) compared with placebo QM on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in human immunodeficiency virus (HIV)-positive subjects with hyperlipidemia or mixed dyslipidemia

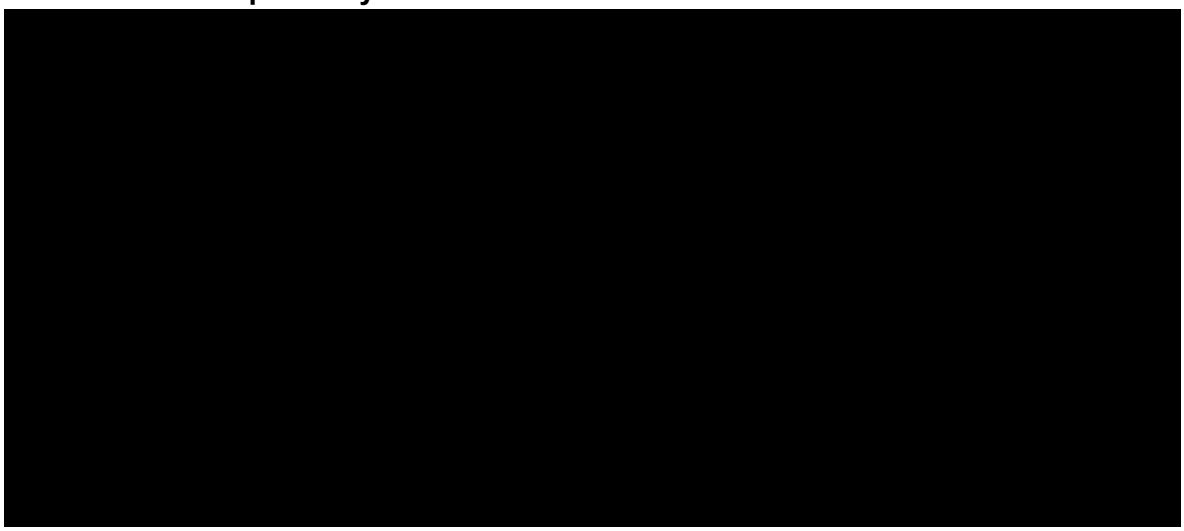
1.2 Secondary

- To assess the effects of 24 weeks of SC evolocumab QM compared with placebo QM on change from baseline in LDL-C, and percent change from baseline in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol (TC), lipoprotein(a) [Lp(a)], triglycerides, HDL-C, and very low-density lipoprotein cholesterol (VLDL-C), in HIV-positive subjects with hyperlipidemia or mixed dyslipidemia
- To assess the effects of 24 weeks of SC evolocumab QM compared with placebo QM on percent of subjects attaining LDL-C < 70 mg/dL (1.8 mmol/L) in HIV-positive subjects with hyperlipidemia or mixed dyslipidemia
- To assess the effects of 24 weeks of SC evolocumab QM compared with placebo QM on percent of subjects attaining a 50% reduction in LDL-C from baseline in HIV-positive subjects with hyperlipidemia or mixed dyslipidemia

1.3 Safety

- To evaluate the safety and tolerability of SC evolocumab QM compared with placebo QM in HIV-positive subjects with hyperlipidemia or mixed dyslipidemia

1.4 Exploratory



2. BACKGROUND AND RATIONALE

2.1 Disease

Approximately 35 million individuals are living with HIV worldwide, with 1.3 million in the United States (Kohli and Giugliano 2013). In countries with access to highly active antiretroviral therapy, the prognosis of HIV infection has changed with mortality from

acquired immunodeficiency syndrome (AIDS)-related causes declining while non-AIDS related causes, including cardiovascular disease (CVD), have risen. HIV-infected patients have an increased risk of CVD as evidenced by increased rate of myocardial infarction (MI) after accounting for age and other comorbidities (Triant et al, 2007).

In the Veterans Aging Cohort Study Virtual Cohort, HIV-positive veterans had an almost 50% greater risk of incident MI compared with uninfected veterans after statistical adjustment for Framingham risk, comorbidities, and substance abuse (Freiberg et al, 2013). A study by the Boston healthcare system showed a 20% higher risk of ischemic stroke in HIV positive versus matched HIV negative controls, adjusted for demographics and stroke risk factors. This study also linked a higher viral load to increased stroke risk (Chow et al, 2012). In addition, a worse outcome after MI has been reported among HIV-positive patients when compared to the general population (Carballo et al, 2015).

By the year 2015, it is estimated that over half of HIV-infected individuals will be aged 50 years and older, and CVD will therefore become even more important in this patient population.

The etiology of CVD in HIV-infected patients is multifactorial. HIV infected patients have higher rates of significant comorbidities including dyslipidemia, diabetes, hypertension, and smoking compared with non-HIV infected patients (Triant et al, 2007; Boccara et al, 2013). HIV-infected patients also have higher levels of inflammatory markers including interleukin-6 (IL-6), high sensitivity C-reactive protein (hsCRP), D-Dimer, and soluble cell differentiation antigen sCD14 (Kuller et al, 2008; Neuhaus et al, 2010).

The Strategies for Management of Antiretroviral Therapy (SMART) Study showed a higher rate of CVD events in patients who discontinued antiretroviral treatment compared with patients on continuous therapy, with a hazard ratio of 1.57 (El-Sadr et al, 2006). In groups experiencing treatment interruption, the levels of the inflammatory cytokine IL-6 and the coagulation marker D-dimer were significantly elevated. Markers of inflammation were also related with the changes in HIV-RNA levels in other treatment interruption studies (Calmy et al, 2009). In addition, these 2 markers showed a statistically signification correlation with death. Elevations of IL-6 have also been statistically associated with the development of CVD (Kuller et al, 2008).

In addition to the increased risk of CVD attributed directly to HIV infection, HIV therapy itself, particularly protease inhibitors (PI), are also linked to increased CVD risk. HIV therapy has been shown to promote adipocyte dysfunction which leads to a lipodystrophy syndrome (Carr 2000; Grinspoon 2005; Capeau 2007; Boccara et al, 2010; Caron-Debarle et al, 2010). The lipodystrophy syndrome is manifested as increased visceral fat, elevated triglycerides, and low HDL-C. Increased rates of insulin resistance and diabetes mellitus, in addition to lipodystrophy, have also been reported in HIV-infected patients. (Carr et al, 1999; Periard et al, 1999; Grinspoon 2005). These factors demonstrate the etiology and pathophysiology of increased CVD risk seen in HIV-infected patients is multifactorial and includes HIV infection itself, therapy for HIV including PI therapy, inflammation, and traditional cardiac risk factors including dyslipidemia.

In an observational cohort study of HIV-infected patients, statin therapy contributed to the reduction of all-cause mortality (Rasmussen et al, 2013). Randomized, controlled trial data demonstrating statin reduction in cardiovascular mortality in HIV subjects is not available although a trial using pitavastatin is now ongoing. In the HIV population, those patients treated with statins appear to be relatively resistant to statin effects as evidenced by lower than expected decreases in TC and LDL-C (Johns et al, 2007; Silverberg et al, 2009).

2.2 Amgen Investigational Product Background

Recycling of the hepatic cell surface LDLR plays a critical role in regulating serum LDL-C levels. PCSK9 binds to the LDLR and downregulates hepatic cell surface LDLR, which, in turn, leads to increased levels of circulating LDL-C. Humans with PCSK9 loss-of-function mutations have cholesterol levels lower than normal and reduced incidence of coronary heart disease (Abifadel et al, 2009). Evolocumab (formerly referred to as AMG 145) is a fully human monoclonal immunoglobulin G2, developed at Amgen Inc., that specifically binds to PCSK9, preventing its interaction with the LDLR. The inhibition of PCSK9 by evolocumab leads to increased LDLR expression and subsequent decreased circulating concentrations of LDL-C.

Refer to the Evolocumab Investigator's Brochure for more information on evolocumab.

2.3 Rationale

It has been shown that HIV-infected patients are at higher risk of CVD and have limitations with statin therapy including possible statin resistance, and elevations of PCSK9 are seen in chronic inflammatory states including HIV infection. Treatment with

an anti-PCSK9 monoclonal antibody is therefore a plausible target for LDL-C reduction in HIV-infected individuals.

It is anticipated that evolocumab may be used in HIV-infected individuals who cannot achieve optimal LDL-C despite the use of maximally tolerated statin therapy or who are intolerant to statin **or for whom statin is contraindicated**. Therefore, understanding the safety and efficacy of evolocumab in patients with HIV is important.

For further details on evolocumab efficacy and safety results refer to the Evolocumab Investigator's Brochure.

2.4 Clinical Hypotheses

Subcutaneous evolocumab QM will be well tolerated and will result in greater reduction of LDL-C, defined as percent change from baseline at week 24, compared with placebo QM in HIV-positive subjects with hyperlipidemia or mixed dyslipidemia.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 3b, multicenter, double-blind, randomized, placebo-controlled study with an open-label extension period designed to assess the efficacy and safety of evolocumab in HIV-positive subjects with hyperlipidemia and/or mixed dyslipidemia. Treatment with baseline HIV and lipid-lowering (if applicable) medications being taken at randomization will continue throughout the clinical study. The study consists of 3 periods:

- Screening (to ensure tolerance of SC injections, includes a placebo injection)
- Double-blind treatment period
- Open-label extension period

Subjects will undergo screening procedures, including laboratory assessments and a screening placebo injection, before being randomized 2:1 into the following treatment groups for the double-blind treatment period:

- SC evolocumab 420 mg QM
- SC placebo QM

The overall sample size will be approximately 450 subjects, with approximately 300 subjects in the evolocumab group. Randomization will be stratified by entry statin treatment (yes/no) and **by** hepatitis C status (yes/no). **The size of the subgroup not on statin therapy is expected to be approximately 10% and no more than 20% of the**

subjects. This enrollment projection is expected to be reflective of clinical practice.

The double-blind period will be 24 weeks, after which subjects who received a dose of investigational product (IP) at week 20 will continue in an open-label period during which all subjects will be treated with QM evolocumab. The open-label period will continue up through the end of study (EOS) visit at week 52.

SC evolocumab and placebo will be administered QM at the study site or appropriate non-investigator site settings (eg, at the subject's home) by automated mini-doser (AMD**; referred to in the United States as an "on-body infuser prefilled cartridge"**) or by spring-based prefilled autoinjector/pen (AI/pen).

3.2 Number of Sites

Approximately **75** sites globally will participate in this study. Sites that do not enroll subjects within 3 months of site initiation may be closed.

3.3 Number of Subjects

Approximately 450 subjects will be enrolled, with approximately 300 subjects in the evolocumab group.

3.4 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

Including the screening, study treatment (double-blind treatment and open-label), and follow-up, the maximal total duration of study participation for a subject will be 56 weeks. After signing the informed consent, subjects should be randomized after 4 weeks (± 1 week) of screening.

3.5.2 End of Study

The primary completion is defined as the date when the last subject has completed assessments for week 24.

The end of trial is defined as the time when the last subject has completed the assessments for week 52.

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of

screening). This log may be completed and updated via an interactive voice response system (IVRS)/interactive web response system (IWRS).

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion and Exclusion Criteria

4.1.1 Inclusion Criteria

101 Subject has provided written informed consent

102 Male or female ≥ 18 years of age at signing of informed consent

103 Known HIV infection with stable HIV therapy for ≥ 6 months prior to randomization and not expected to change during the duration of study participation. Stable HIV therapy is defined as no new agents added and no dose change of any HIV drug within 6 months prior to randomization

104 Cluster of differentiation 4 (CD4) ≥ 250 cells/mm^3 for ≥ 6 months prior to randomization

105 HIV viral load ≤ 50 copies/mL at screening and ≤ 200 copies/mL for ≥ 6 months prior to randomization

106 Subject on stable **lipid-lowering therapy** for ≥ 4 weeks prior to randomization **and not expected to change during the duration of study participation**. **Subjects should be on** maximally tolerated dose of statin**s. For some subjects, "maximally tolerated" may indicate no statin at all due to statin intolerance or contraindication to statin therapy. Statin intolerance or contraindication must be documented. A subject with statin intolerance must be evidenced by the following:**

a. Must have tried at least 2 statins with failure to at least 1 of the statins at an average daily dose at or below the following doses due to intolerable myopathy (ie, myalgia [muscle pain, ache, or weakness without creatine kinase elevation]), myositis (muscle symptoms with increased creatine kinase levels), or rhabdomyolysis (muscle symptoms with marked creatine elevation, as defined under "b"):

- **atorvastatin: 10 mg**
- **simvastatin: 10 mg**
- **pravastatin: 40 mg**
- **rosuvastatin: 5 mg**
- **lovastatin: 20 mg**
- **fluvastatin: 40 mg**
- **pitavastatin: 2 mg**

AND

b. Symptoms resolved or improved when statin dose was decreased or discontinued

For subjects that developed rhabdomyolysis, defined as creatine kinase > 10 × upper limit of normal (ULN), failure of only 1 statin at any dose is acceptable.

107 **Subject without known clinical atherosclerotic CVD (ASCVD): fasting LDL-C of ≥ 100 mg/dL (2.6 mmol/L) or non-HDL-C of ≥ 130 mg/dL (3.4 mmol/L) as determined by the central laboratory at screening. Subject with known clinical ASCVD:** fasting LDL-C of ≥ 70 mg/dL (1.8 mmol/L) or non-HDL-C of ≥ 100mg/dL (2.6 mmol/L) as determined by the central laboratory. **Clinical ASCVD is defined as a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin.**

108 Fasting triglycerides ≤ 600 mg/dL (6.8 mmol/L) as determined by central laboratory during screening

109 Subject tolerates screening placebo injection

4.1.2 Exclusion Criteria

201 Subject taking a combination of background lipid-lowering therapy and HIV therapy known to have significant drug-drug interaction as per Table 2

202 New York Heart Association III or IV heart failure, or last known left ventricular ejection fraction < 30%

203 Known opportunistic infection/AIDS defining illness (including but not limited to candidiasis of bronchi, trachea, esophagus, or lungs, invasive cervical cancer, coccidioidomycosis, cryptococcosis, chronic intestinal (> 1-month duration) cryptosporidiosis, cytomegalovirus disease (particularly cytomegalovirus [CMV] retinitis), HIV-related encephalopathy, herpes simplex: chronic ulcer(s) (> 28 days duration); or bronchitis, pneumonitis, or esophagitis, histoplasmosis, chronic intestinal (> 28 days duration) isosporiasis, Kaposi's sarcoma, lymphoma, mycobacterium avium complex, tuberculosis, pneumocystis carinii pneumonia, recurrent pneumonia, progressive multifocal leukoencephalopathy, salmonella septicemia, toxoplasmosis of brain, or wasting syndrome due to HIV within 1 year prior to randomization

204 Myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft or stroke within 3 months prior to randomization

205 Type 1 diabetes, new-onset (hemoglobin A1c [HbA1c] ≥ 6.5% or fasting plasma glucose ≥ 126 mg/dL at screening without known diagnosis) or poorly controlled (HbA1c ≥ 10%) type 2 diabetes by central laboratory during screening

206 Uncontrolled hypertension defined as sitting systolic blood pressure > 180 mmHg or diastolic blood pressure > 110 mmHg during screening

207 Subject has taken a cholesterylester transfer protein inhibitor in the last 12 months prior to randomization

208 Moderate to severe renal dysfunction, defined as an estimated glomerular filtration rate < 30 mL/min/1.73 m^2 during screening

209 Persistent active liver disease or hepatic dysfunction defined as Child-Pugh score of C. Stable (in the opinion of the primary investigator and with aspartate aminotransferase [AST] and alanine aminotransferase [ALT] < 5 times ULN and not expected to require new treatment[s] during study) chronic hepatitis C of at least 1 year duration prior to randomization is allowed

210 Female subject of childbearing potential not willing to use acceptable method(s) of effective birth control during treatment with IP and for an additional 15 weeks after the end of treatment with IP. Female subjects of non-childbearing potential are not required to use contraception during the study and include those who have had a hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or who are postmenopausal.

Postmenopausal is defined as 12 months of spontaneous and continuous amenorrhea in a female ≥ 55 years old; or age < 55 years but no spontaneous menses for at least 2 years; or age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy) and with postmenopausal gonadotropin levels (luteinizing hormone and follicle stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved

Acceptable methods of effective birth control include:

- true sexual abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception]),
- surgical contraceptive methods (vasectomy or bilateral tubal ligation/occlusion),
- use of hormonal birth control methods (oral, intravaginal, transdermal, injectable, or implantable),
- intrauterine devices,
- intrauterine hormonal releasing system, or
- 2 barrier methods (each partner must use 1 barrier method) and at least 1 of barrier methods must include spermicide (males must use a condom; females must choose either a diaphragm OR cervical cap OR contraceptive sponge). If spermicide is not available in the country or region, the 2-barrier method without spermicide is acceptable.

Note: Additional medications given during treatment with evolocumab may alter the contraceptive requirements. These additional medications may require an increase in the number of contraceptive methods, the change in type of contraceptive methods and/or length of time that contraception is to be utilized or length of time breastfeeding is to be avoided. The investigator is to discuss these contraceptive changes with the study subject.

211 Female subject is pregnant or breast feeding, planning to become pregnant or planning to breastfeed during treatment with IP and/or within 15 weeks after the end of treatment with IP

212 Malignancy (except non-melanoma skin cancers, cervical in-situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma) within the last 5 years prior to randomization

213 Subject has previously received evolocumab or any other therapy to inhibit PCSK9

214 Currently receiving treatment in another investigational device or drug study, or < 30 days before randomization since ending treatment on another investigational device or drug study(s) or planning to receive other investigational procedures while participating in this study

215 Subject has known sensitivity to any of the active substances or their excipients to be administered during dosing, eg, carboxymethylcellulose

216 Subject likely to not be available to complete all protocol-required study visits or procedures, and/or to comply with all required study procedures to the best of the subject's and investigator's knowledge

217 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures, or completion

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form (ICF), and all other subject information and/or recruitment material, if applicable (see Section 11.2). All subjects must personally sign and date the ICF before commencement of study specific activities/procedures.

A subject is considered enrolled upon randomization. The investigator is to document this decision and date, in the subject's medical record and in the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (defined as the point at which the subject signs the ICF) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned **via** IVRS/IWRS. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

Subjects who are unable to complete or meet eligibility on initial screening will be permitted to re-screen, except for subjects **who do not meet inclusion criterion 107** (see Section 7.2.2).

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened. This number will not necessarily be the same as the randomization number assigned for the study.

5.1 Randomization/Treatment Assignment

Subjects who tolerate the placebo injection, complete all screening procedures, and successfully meet all eligibility criteria at the end of screening will be randomized via IVRS/IWRS and will return to the study site for day 1 procedures while continuing their background HIV and lipid-lowering treatment (if applicable).

Subjects will be randomized in 2:1 ratio to 2 treatment groups (evolocumab and placebo, respectively) in a double-blind manner. The randomization will be stratified by entry statin treatment and hepatitis C status.

Subjects can only be randomized 1 time for this study. The randomization date **(study day 1)** is to be documented in the subject's medical record and on the enrollment CRF. Randomization numbers will be provided to the site through an IVRS/IWRS.

5.2 Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment should only be unblinded when knowledge of the treatment is essential for the further management of the subject on this study. Unblinding at the study site for any other reason will be considered a protocol deviation.

Refer to the Investigational Product Instruction Manual (IPIM) for a description regarding how responsible pharmacists and investigators will access treatment information via the IVRS/IWRS, in the event that there is a need to break the blind.

The investigator is strongly encouraged to contact the Amgen Clinical Study Manager before unblinding any subject's treatment assignment, but must do so within 1 working day after the event.

6. TREATMENT PROCEDURES

6.1 Classification of Product(s) and/or Medical Device(s)

The Amgen IP used in this study is evolocumab and matching placebo. In several countries, IP is referred to as investigational medicinal product (IMP). In this document, IMP will be referred to as IP.

The investigational medical device is the AMD, or the spring based prefilled AI/pen.

Note: Ancillary device(s) (ie, any medical device[s] not under study) are described in Section 6.6.

The IPIM, a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of evolocumab and placebo.

6.2 Investigational Product

Evolocumab and matching placebo will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures.

Evolocumab 420 mg and placebo SC will be supplied as an AMD or AI/pen:

- An AMD as a single use, disposable, on-body electro-mechanical injection device that is co-packaged with a prefilled Crystal Zenith cartridge containing 3.5 mL deliverable volume of 120 mg/mL evolocumab or an identical volume of placebo.
- An AI/pen as a single use, disposable, handheld mechanical (spring-based) for fixed dose, SC injection of 140 mg evolocumab in 1.0 mL deliverable volume or an identical volume of placebo.

Placebo will be presented in identical containers and stored/packaged the same as evolocumab.

6.2.1 Dosage, Administration, and Schedule

6.2.1.1 Screening

During screening, subjects will undergo SC placebo injection with the device to be used during the study (AMD or AI/pen). Subjects must tolerate the placebo injection prior to randomization.

6.2.1.2 Double-blind Treatment Period

The IP (420 mg evolocumab or matching placebo via AMD, or AI/pen) will be administered QM on day 1, week 4, week 8, week 12, week 16, and week 20.

SC evolocumab and placebo will be administered at the study site or in an appropriate non-clinic setting (eg, at the subject's home). Observed, in-clinic dosing should occur at day 1 and week 20. Subjects who do not wish to self-inject at home may return to the clinic for injection. **See Table 3 for the schedule of in-clinic visits.**

The IP will be administered SC in accordance with instructions in the IPIM and the Information for Use (IFU). The subject (or designee, if not a qualified healthcare professional) must have demonstrated competency, as per site judgment, at administration of SC injections before self-administration is permitted: the first

self-administered dose by the subject (or designee, if not a healthcare professional) must be administered at the site under the supervision of a healthcare provider. If IP is to be administered during the study visit, administration must occur after all other procedures have been completed.

When IP is mandated to be administered at the study site, the date and time of administration, the body location of the injection, and whether the injection was administered fully, partially, or not at all, in addition to the reason for a partial/lack of injection, are to be provided. When IP can be administered at an appropriate non-clinic setting (eg, at the subject's home), at a minimum, the dates the devices were dispensed and returned, the number of devices dispensed and returned, and number of devices administered fully, partially, or not at all, in addition to the reason for a partial/lack of injection, must be provided.

When IP is mandated to be administered at the study site, the date and completion time of administration, the body location of the injection, and whether the injection was administered fully, or partially, or not at all administered, in addition to the reason for a partial/lack of injection, are to be recorded on each subject's CRF provided. When IP can be administered at an appropriate non-clinic setting (eg, at the subject's home), a non-investigator site location, at a minimum, the dates that the devices were dispensed and the used devices were returned, the number of devices dispensed and returned, and number of devices administered fully, partially, or not at all, in addition to the reason for a partial/lack of injection, must be provided whether each device was returned fully or partially used are to be recorded on each subject's CRF.

Overdose with this product has not been reported.

6.2.1.3 Open-label Period

Subjects who receive a dose of IP at week 20 will continue in an open-label period. During the open-label period, all subjects will be treated with 420 mg evolocumab via AMD, or AI/pen. Dosing at week 24 is expected to be in-clinic while dosing for weeks 28, 32, 36, 40, 44, and 48 is expected to be in an appropriate non-clinic setting (eg, at the subject's home**, even on weeks with in-clinic visits**); **however,** subjects who do not wish to self-inject at home may return to the clinic for injection.

6.2.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

No dose adjustments are allowed in this study. If, in the opinion of the investigator, a subject is unable to tolerate a specific dose of IP, that subject will discontinue IP but will continue to return for all other study procedures and measurements until the EOS visit.

If a dose of evolocumab is missed, administration should occur as soon as possible if there are > 7 days until the next scheduled dose. If there are less than 7 days before the next scheduled dose, the missed dose should be omitted and the next dose should be administered according to the original schedule.

6.3 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], AST, ALT, total bilirubin [TBL]) **and/or international normalized ratio (INR)** and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen IP or other protocol-required therapies as specified in the Guidance for Industry Drug-Induced Liver Injury (DILI): Premarketing Clinical Evaluation (July 2009).

6.3.1 Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules (Table 1) apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and Parvovirus)
- Right-sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis

- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis
- Nonhepatic causes (eg, rhabdomylosis, hemolysis)

Amgen IP (evolocumab/placebo) and other protocol-required therapies should be discontinued permanently and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible DILI.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.3.2).

Table 1. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
Total bilirubin	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5 (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or total bilirubin values > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x ULN at any time	--

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; ULN=upper limit of normal.

6.3.2 Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then evolocumab/placebo should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.3.1) should never be rechallenged.

6.4 Other Protocol-required Therapies

Other protocol-required therapies are stable HIV therapy and stable dose of lipid-lowering therapy, if applicable, as defined in subject eligibility (Section 4.1).

Other protocol-required therapies are not provided or reimbursed by Amgen (except if required by local regulation). The investigator will be responsible for obtaining commercially available supplies of these protocol-required therapies.

Additional details regarding these protocol-required therapies are provided in the IPIM.

6.5 Concomitant Therapy

Throughout the study, the investigator may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.8.

6.6 Medical Devices

The AMD or prefilled AI/pen used in this study will be provided by Amgen. Additional details for the AMD or AI/pen are provided in the IPIM and IFU.

Ancillary medical devices (eg, syringes, sterile needles, alcohol prep pads), which are not considered test articles, may be used in the conduct of this study as part of standard care. These devices that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

6.7 Product Complaints

A product complaint is defined by Amgen as any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s)**,** device(s**), or combination products** after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any

drug(s) or device(s) provisioned and/or repackaged/modified by Amgen. Drugs or devices include evolocumab/placebo and AMD or prefilled AI/pen.

Concerns or irregularities about the packaging, appearance or usage of the IP or device are to be reported to Amgen within 24 hours of discovery or notification of the concern or irregularity. Should any such concerns or irregularities occur please do not use the IP until Amgen confirms that it is permissible to use.

Examples of potential product complaints that need to be reported to Amgen include, but are not limited to:

- broken container or cracked container;
- subject or healthcare provider cannot appropriately use the product despite training (eg, due to malfunction of the AMD or AI/pen);
- missing labels, illegible labels, incorrect labels, and/or suspect labels;
- change in IP appearance (eg, color change or visible presence of foreign material);
- unexpected quantity or volume (eg, amount of fluid in the study drug prefilled cartridge), or
- evidence of tampering or stolen material.

If possible, please have the suspect product available for examination when making a product complaint and maintain the IP at appropriate storage conditions until further instructions are received from Amgen.

The investigator is responsible for ensuring that all product or device complaints observed by the investigator or reported by the subject that occur after signing of the ICF through 30 days after the last dose of IP or EOS, whichever is later, are reported to Amgen within 24 hours of discovery or notification of the product complaint.

Additional details regarding the identification and reporting of any product complaint(s) associated with an IP or non-investigational product(s) or device(s) supplied by Amgen are provided in the IPIM.

6.8 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

The following treatments are not permitted during the study:

- any investigational therapies other than study-provided IP

The following treatments are not permitted during the blinded portion of the study:

- any lipid-lowering therapies not taken at the time of screening and enrollment **(unless required in response to HIV worsening; see Section 9.1.2.1)**.

Please contact the Amgen medical monitor or designee if any of these therapies should be initiated during the blinded portion of the study. Note that a change in lipid-lowering therapy does not necessarily require ending IP administration.

During the open-label period, adjustments to background lipid-lowering therapy due to results of the unblinded lipid panel (ie, asymptomatic LDL-C) will not be allowed. Changes to background lipid-lowering therapy for other reasons such as adverse events are allowed during the open-label period.

The following treatments are not recommended in subjects treated with statins metabolized by cytochrome P450 (CYP) 3A4 (eg, simvastatin or atorvastatin) because of their potential impact on metabolism of certain statins:

- medications or foods that are known potent inhibitors of CYP3A (eg, itraconazole, ketoconazole, and other antifungal azoles, macrolide antibiotics erythromycin, clarithromycin, and the ketolide antibiotic telithromycin, HIV or hepatitis C virus (HCV) PI, antidepressant nefazodone and grapefruit juice in large quantities (> 1 quart daily [approximately 1 Liter]) should not be used during the study. See Table 2 for additional details.

Table 2. Statin Interactions

Statin	Failure to Adjust Dosage for Concomitant Medications	Use with Contraindicated Medication (Risk X)
Atorvastatin	Atorvastatin > 40 mg while taking boceprevir, simeprevir, or nelfinavir; atorvastatin > 20 mg while taking clarithromycin, telithromycin, itraconazole, fosamprenavir, or ritonavir-boosted darunavir, fosamprenavir, or saquinavir	Concomitant use of atorvastatin with gemfibrozil, posaconazole, telaprevir, or tipranavir
Fluvastatin	Fluvastatin > 20 mg BID while taking fluconazole	Concomitant use of fluvastatin with gemfibrozil
Lovastatin	Lovastatin > 20 mg daily while taking diltiazem or verapamil; lovastatin > 40 mg while taking amiodarone or niaspan	Concomitant use of lovastatin with clarithromycin, erythromycin, telithromycin, itraconazole, nefazodone, posaconazole, voriconazole, HIV protease inhibitors, HCV protease inhibitors (bocepravir, telaprevir), cobicistat, or gemfibrozil
Pitavastatin	Pitavastatin > 1 mg daily with erythromycin or > 2 mg daily with rifampin	Concomitant use of pitavastatin with gemfibrozil
Pravastatin	Pravastatin > 40 mg while taking clarithromycin	Concomitant use of pravastatin with gemfibrozil
Statin	Failure to Adjust Dosage for Concomitant Medications	Use with Contraindicated Medication (Risk X)
Rosuvastatin	Rosuvastatin > 10 mg while taking ritonavir-boosted atazanavir or lopinavir	Concomitant use of rosuvastatin with gemfibrozil
Simvastatin	Simvastatin > 20 mg with amiodarone or amlodipine; simvastatin > 10 mg with diltiazem or verapamil; simvastatin > 40 mg with niaspan	Concomitant use of simvastatin with clarithromycin, erythromycin, telithromycin, itraconazole, nefazodone, posaconazole, voriconazole, HIV protease inhibitors, HCV protease inhibitors (bocepravir, telapravir), cobicistat, or gemfibrozil

BID=twice daily; HCV=hepatitis C virus; HIV=human immunodeficiency virus.

7. STUDY PROCEDURES

Screening assessments and study procedures outlined in this section and in Table 3 can only be performed after obtaining informed consent.

All on-study visits and dosing should be scheduled from day 1 (**randomization and** first IP administration). For example, the week 4 visit is 4 calendar weeks after the study day 1 visit, corresponding to study day 28. When it is not possible to perform the study visit at the specified time point, the visit should be performed within the visit window specified in Table 3. If a study visit is missed or late, including visits outside the visit window, subsequent visits should resume on the original visit schedule. Missed assessments at prior visits should not be duplicated at subsequent visits. With the

exception of screening, all study procedures for a visit should be completed on the same day if possible.

Refer to the applicable supplemental laboratory manuals for detailed collection and handling procedures.

7.1 Schedule of Assessments

Screening assessments and study procedures are outlined in this section and in Table 3 (Schedule of Assessments).

Table 3. Schedule of Assessments

Study Day / Timepoint	Screening 4 (± 1) weeks	Double-Blind Period				Open-Label Period	
		Day 1	Week 12 ± 3 days	Week 20 ± 3 days	Week 24 ± 3 days[a]	Week 36 ± 7 days	EOS Week 52 ± 7 days
General Procedures							
Informed consent	X						
Medical history	X						
Vital signs	X	X	X	X	X	X	X
Safety data reporting[b]	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X
Physical exam	X	X			X		X
Body weight, waist circumference	X				X		X
Body height	X						
Screening placebo injection[c]	X						
Randomization		X					
Central Laboratory							
Fasting lipids, ApoA1, ApoB, Lp(a)	X	X	X		X	X	X
[redacted]		X	X		X	X	X
		X	X		X	X	X
HIV viral load and CD4	X	X	X		X	X	X
Hepatitis C antibodies	X						
Hepatitis C viral load[d]	**X**	X	X		X	X	X
Chemistry	X	X	X		X	X	X

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Footnotes defined on next page of this table

Table 3. Schedule of Assessments

Study Day / Timepoint	Screening 4 (± 1) weeks	Double-Blind Period				Open-Label Period	
		Day 1	Week 12 ± 3 days	Week 20 ± 3 days	Week 24 ± 3 days[a]	Week 36 ± 7 days	EOS Week 52 ± 7 days
Urinalysis	X	X	X		X	X	X
Hematology	X	X	X		X	X	X
Serum pregnancy,[e] **urine pregnancy**,[e] FSH/LH/estradiol[f]	X	**X**	**X**	**X**	X	**X**	X
HbA1c	X		X		X	X	X
Biomarkers (blood)		X	X		X		X
Anti-evolocumab antibodies		X	X		X	X	X
Investigational Product							
IP dispensing		X	X		X	X	
IP reconciliation			X	X	X	X	X
IP administration **(every 4 weeks)**[g]		X	**X**	X	X	**X**	

ApoA1=apolipoprotein A-I; ApoB=apolipoprotein B; CD4=cluster of differentiation 4; EOS=end of study; FSH=follicle-stimulating hormone; HbA1c=hemoglobin A1c; HIV=human immunodeficiency virus; IP=investigational product; LH=luteinizing hormone; Lp(a)=lipoprotein(a); [redacted]

[a] At week 24, final double-blind period assessments will be conducted, and the first dose of open-label study drug will be administered.

[b] Including review for adverse events/serious adverse events/disease-related events/adverse device effects. **Adverse events possibly related to study procedures, adverse device effects and serious adverse events are reported from signing of the informed consent form. All other adverse events are reported from the time of randomization.**

[c] Placebo injection is to occur following determination of eligibility for all other screening parameters.

[d] Hepatitis C viral load will be completed only in hepatitis C-positive subjects.

[e] Pregnancy testing in females of childbearing potential. **Serum pregnancy testing at screening. Urine pregnancy testing at day 1 and weeks 12, 20, 24, 36, and prior to IP administration and at EOS.** Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required by local laws and regulations.

[f] FSH/LH/estradiol only at screening **for menopausal women**.

[g] During the double-blind period, in addition to the in-clinic administration at day 1 and week 20, QM non-clinic IP is expected to be administered 4 times prior to the week 20 visit (ie, at weeks 4, 8,12, and 16). During the open-label period, in addition to the in-clinic administration at week 24, QM non-clinic evolocumab is expected to be administered 6 times prior to the week 52 visit at weeks 28, 32, 36, 40, 44, and 48.

7.2 General Study Procedures

The procedures performed at each study visit are outlined Table 3. Details regarding each type of procedure are provided in subsequent subsections.

Before each study visit where fasting lipid samples are obtained, subjects must be fasting overnight. If the subject is not fasting for the screening or the day 1 visit, no visit procedures are to be performed, and the visit should be rescheduled within the applicable protocol windows. If subject is not fasting after day 1, all procedures except fasting labs and IP administration, if applicable, will be performed and another visit should be scheduled, within the visit window if possible, for sampling for fasting labs and IP administration.

For each study visit when IP is administered at the site, administration must be after completion of blood draw procedures, if applicable.

Subjects will be encouraged to complete all planned visits regardless of their adherence to IP administration.

Refer to the applicable supplemental central laboratory, IVRS/IWRS, IPIM, and study manuals for detailed collection and handling procedures.

7.2.1 Screening Enrollment and Randomization

Subjects who are considered for entry into the study and have the risk and benefits of participating in the study explained will enter screening by signing and dating the ICF for this study. Informed consent must be obtained before completing any other screening procedure.

After the subject signs the written informed consent, the site will screen the subject in order to assess eligibility for participation. Screening should be completed and the subject randomized or screen failed after 4 weeks (± 1 week) of signing the informed consent.

Subjects will undergo SC placebo injection with device anticipated to be used during study (AMD or AI/pen) during screening.

Subjects who tolerate the screening placebo injection, complete all screening procedures successfully, and meet all eligibility criteria at the end of screening will be randomized via IVRS/IWRS and will return to the study site for day 1 procedures while continuing their background HIV and lipid-lowering (if applicable) treatment. Subjects

should be randomized before or on the date of the day 1 visit, and initiate their first dose of IP within 5 days of randomization.

7.2.2 Rescreening

Subjects **who do not meet inclusion criterion 107** are considered screen failures and cannot be rescreened for this study. Suitable subjects who are ineligible at the initial screening for other reasons and have not been randomized can be reconsented and rescreened at a later time, unless they withdraw from screening, provided the study is still enrolling subjects.

For subjects who are rescreened, data from the first screening period will not be used for the analysis. Rescreened subjects who are reconsented will repeat all screening procedures. Rescreened subjects will maintain the originally assigned subject identification number.

7.2.3 Double-blind Treatment Period

Visits will occur per the Schedule of Assessments (Table 3) during the **double-blind** period from day 1 (week 1, baseline) through week 24. Visits during the treatment period must be completed within ± 3 days of the target visit date. For visits with IP administration at the study site, administration should be the last procedure to be performed during each visit.

If a subject withdraws from the study early, all efforts should be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. If possible, the procedures of the week 24 visit should be completed at the time of withdrawal.

7.2.4 Open-label Period

Subjects who receive a dose of IP at week 20 will continue in an open-label period. **They will receive their first dose of open-label IP at the week 24 visit.** Visits will **then** occur per the Schedule of Assessments (Table 3) at weeks 36 and 52. Visits during the open-label period must be completed within ± 7 days of the target visit date.

7.2.5 End of Study / Safety Follow-up

At week 52 or 30 days after the last administration of IP, whichever is later, a safety follow-up is scheduled to occur. This safety follow-up can be an in-person visit to the study center or another contact with the subject. **If the end-of-study visit is < 30 days after the last dose of IP, the subject will be contacted (eg, by phone) at 30 (± 7) days after last IP for safety follow-up.**

7.3 Description of Study Procedures

The sections below provide a description of the individual study procedures.

7.3.1 Informed Consent

All subjects must sign and personally date the IRB/IEC approved informed consent before any study specific procedures are performed.

7.3.2 Demographics

Demographic data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness. Additionally demographic data will be used to study the impact on biomarkers variability of the protocol-required therapies.

7.3.3 Medical History

The investigator or designee will collect a complete medical history covering the period within 120 days prior to randomization. Additionally, a targeted cardiovascular and HIV history not limited to 120 days prior to randomization will be collected. Targeted cardiovascular history including, but not limited to, cardiovascular risk factors, history of CVD, revascularization procedures, family history, and potential familial hypercholesterolemia diagnostic criteria will be collected. Targeted HIV history including, but not limited to, duration, HIV complications, and occurrence of opportunistic infections or AIDS-defining illness from diagnosis will be collected.

7.3.4 Vital Signs

The following measurements must be performed: blood pressure and heart rate. The subject must be in a seated position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. The appropriate size cuff should be used. The **same arm and same** position should be used throughout the study and documented on the vital sign CRF.

During screening, blood pressure measurements can be repeated if the previous reading was outside of the eligibility range. The repeat blood pressure measurement should be taken at least 2 minutes after the previous one.

7.3.5 Safety Data Reporting

Adverse events, serious adverse events, disease-related events, and adverse device effects observed by the investigator or reported by the subject will be collected at all study visits from **randomization** through EOS as detailed in Section 9. Adverse events

possibly related to study procedures, adverse device effects and serious adverse events are collected during screening.

7.3.6 Prior Therapies, Substance Use History, and Concomitant Medications

Prior general and targeted therapies (eg, statins and HIV therapy) taken within 120 days prior to randomization should be collected with the following information: therapy name, indication, dose, unit, frequency, route, start date, and stop date.

If a targeted therapy is begun, discontinued, or changed during study, in addition to updates for the above information, the reason for adjusting medication (adverse event, worsening of underlying condition, noncompliance etc.) should be recorded.

Concomitant therapies are to be collected from the signing of the informed consent through the EOS, and should include the therapy name, indication, dose, unit, frequency, route, start date, and stop date. Concomitant medications include over-the-counter products and vitamins administered while the subject is on study.

7.3.7 Physical Examination

A physical examination will be conducted as per standard of care. Physical examination findings should be recorded on the appropriate CRF (eg, height, weight, BMI, etc.)

7.3.8 Body Weight, Waist Circumference, and Height

Body weight in kilograms and height in centimeters should be measured without shoes.

For measurement of waist circumference, subjects should wear minimal clothing to ensure that the measuring tape is correctly positioned. Subjects should stand erect with the abdomen relaxed, arms at the sides, feet together and with their weight equally divided over both legs. To perform the waist measurement, the lowest rib margin is first located and marked with a pen. The iliac crest is then palpated in the midaxillary line. It is recommended to apply an elastic tape horizontally midway between the lowest rib margin and the iliac crest, and tie firmly so that it stays in position around the abdomen about the level of the umbilicus. The elastic tape thus defines the level of the waist circumference, which can then be measured by positioning the measuring tape over the elastic tape. Subjects are asked to breathe normally, and to breathe out gently at the time of the measurement to prevent them from contracting their muscles or from holding their breath. Measurements should be performed using the same procedure throughout the study. The reading is taken to the nearest centimeter or half an inch and entered in the source document.

7.4 Laboratory Assessments

All laboratory samples will be sent to the central laboratory**, except for samples for urine pregnancy tests, which will be conducted by the local laboratory**. Concentration values are provided in mmol/L for investigator convenience. Conventional concentrations (mg/mL) will be used for the protocol, including for eligibility determination. The estimated glomerular filtration rate (eGFR) will be calculated by the central laboratory and provided to the site for eligibility determination.

The central laboratory will provide a study manual that outlines handling, labeling, and shipping procedures for all samples.

All blood samples will be obtained by venipuncture before IP administration. The date and time of sample collection will be recorded in the source documents at the site. Specific analytes for serum chemistry, urinalysis, hematology, and other labs to be conducted on blood and urine samples are shown in Table 4. Although not specifically listed, additional components, abnormal, and/or atypical cells will also be reported if present.

Table 4. Analyte Listing

Chemistry	Urinalysis	Hematology	Other Labs
Sodium Potassium Chloride Bicarbonate Total protein Albumin Calcium Magnesium Phosphorus Fasting glucose Fasting insulin BUN or Urea Creatinine Uric acid Total bilirubin Direct bilirubin CK ALP LDH AST ALT eGFR	Specific gravity pH Blood Protein Glucose Bilirubin WBC RBC Epithelial cells Bacteria Casts Crystals **Urine pregnancy test (females of childbearing potential)**	CD4 Hemoglobin Hematocrit RBC RDW MCV MCH MCHC WBC Platelets Differential • Neutrophils • Bands • Eosinophils • Basophils • Lymphocytes • Monocytes	Fasting lipids • Total cholesterol • HDL-C • LDL-C • Triglycerides • VLDL-C • Non-HDL-C ApoA1 ApoB Lp(a) [redacted] HbA1c Serum pregnancy test (females of childbearing potential) FSH/LH)/ Estradiol (if needed per exclusion 210) HCV antibody HCV viral load HIV viral load

7.4.1 Blinding of Laboratory Test Results

In order to protect the blinding of the double-blind treatment period, the following labs will be blinded postscreening until unblinding of the clinical database and not reported to sites except as noted below:

- Blinded to the Amgen study team and site staff: lipid panel, ApoA1, ApoB, Lp(a), and [redacted]
- Blinded to the site staff: insulin, [redacted]. Analyses of [redacted] may not be completed until EOS so results are not expected to be available during the trial.

In addition, investigators should not perform non-protocol testing of these analytes during a subject's study participation and until at least 12 weeks after the first dose of unblinded evolocumab at week 24 (ie, week 36 visit).

The following central laboratory results during open-label period will be reported to the sites for the week 36 through week 52 visits: lipid panel, ApoA1, ApoB, Lp(a).

7.4.2 Pregnancy Tests

All females, except those who are confirmed surgically sterile or at least 2 years postmenopausal or 1 year postmenopausal if ≥ 55 years old, must have a negative serum pregnancy test at **screening**, prior to administering the first dose of evolocumab/placebo. The central laboratory will provide the **screening** pregnancy tests.

Urine pregnancy tests will be performed on day 1 and on weeks 12, 20, 24, and 36 before IP administration and at EOS.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required by local laws and regulations.

7.5 Antibody Testing Procedures

Blood sample(s) for antibody testing are to be collected at the time points shown in Table 3 for the measurement of anti-evolocumab binding antibodies. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. Additional blood samples may be obtained to rule out anti-evolocumab antibodies during the study.

7.6 Biomarker Development

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Biomarker development can be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease severity. Amgen may attempt to develop test(s) designed to identify subjects most likely to respond positively or negatively to evolocumab.

Blood samples are to be collected for biomarker development at day 1, week 12, week 24, and week 52. Refer to the laboratory manual for detailed collection and handling procedures for all biomarker development samples.

Biomarkers related to, but not limited to, [redacted] may be studied.

7.7 Pharmacogenetic Studies

No additional blood will be collected for the pharmacogenetic analyses. If the subject consents to the optional pharmacogenetic portion of this study, deoxyribonucleic acid (DNA) analyses may be performed. These optional pharmacogenetic analyses focus on inherited genetic variations to evaluate their possible correlation to the disease and/or responsiveness to the therapies used in this study. The goals of the optional studies include the use of genetic markers to help in the investigation of cardiovascular disease, hyperlipidemia and other metabolic disorders and/or to identify subjects who may have positive or negative response to evolocumab.

7.8 Sample Storage and Destruction

Any blood sample collected according to the Schedule of Assessments (Table 3) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the underlying inflammatory conditions, the dose response and/or prediction of response to evolocumab, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetic, biomarker development, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining blood samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.3 for subject confidentiality.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue receiving IP and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from IP or other protocol-required therapies and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 3) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 3) and the level of follow-up that is agreed to by the subject (eg, in person, by

telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from IP and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen IP and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

8.3 Reasons for Removal From Treatment or Study

8.3.1 Reasons for Removal From Treatment

Reasons for removal from protocol-required IP or procedural assessments include any of the following:

- subject request
- subject request to end IP administration
- safety concern (eg, due to an adverse event, pregnancy in a female subject)
- death
- lost to follow-up
- administrative decision by Amgen (other than subject request, safety concern, or lost to follow-up)
- decision by the primary investigator/physician

8.3.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- decision by Amgen
- withdrawal of consent from study
- death
- lost to follow-up

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definition of Safety Events

9.1.1 Disease-related Events

Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. In this study, subjects are at risk for or are known to have cardiovascular disease. Therefore, disease-related events potentially include manifestations and complications of atherosclerotic vascular disease such as coronary artery disease, angina, MI, ischemic stroke, transient ischemic attack, carotid artery disease, peripheral vascular disease, and testing suggesting progression of atherosclerotic vascular disease. Such events do not meet the definition of an adverse event unless assessed to be more severe than expected for the subject's condition.

Disease-related events and/or disease related outcomes that do not qualify as **adverse events or** serious adverse events:

- An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a disease-related event.
- Death due to the disease under study is to be recorded on the Event CRF.

A disease-related event that would qualify as an adverse event or serious adverse event is an event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition or an event for which the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol required therapies and disease worsening. This must be reported as an adverse event or serious adverse event.

9.1.2 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected, and/or has an association with a significantly worse outcome than expected. A pre-existing condition that has not worsened more than anticipated (ie, more than usual fluctuation of disease) during the study or involves an

intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

The criteria for grade 4 in the Common Terminology Criteria for Adverse Events (CTCAE) grading scale differs from the regulatory criteria for serious adverse events. It is left to the Investigator's judgment to report these grade 4 abnormalities as serious adverse events.

9.1.2.1 Worsening of HIV Disease

HIV worsening will be captured as an adverse event. Because evolocumab is not expected to have any interaction with antiretroviral therapy or viral load or consequences of HIV infection, no specific actions with respect to study participation (including investigational product) are expected of the investigator. Should a subject's viral load change or HIV infection worsen, the investigator is expected to manage HIV infection or any other concomitant illnesses per his or her clinical judgment. Background lipid-lowering therapy is expected to be stable. However, in the case of HIV worsening, because of potential drug–drug interaction between statins and antiretroviral therapy, changing background lipid-lowering therapy is left to the judgment of the investigator.

9.1.3 Adverse Device Effects

An adverse device effect is any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

9.1.4 Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria (unless it meets the definition of a disease-related event provided in Section 9.1.1):

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

A disease-related event is to be reported as a serious adverse event if:

- the subject's pre-existing condition becomes worse than what the investigator would consider typical for a patient with the same underlying condition, or
- if the investigator believes a causal relationship exists between the IMP/protocol-required therapies and the event,
- and the event meets at least 1 of the serious criteria above.

An adverse event would meet the criterion of "requires hospitalization," if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event." Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, DILI (see Appendix A for drug-induced liver injury reporting criteria), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Safety Event Reporting Procedures

9.2.1 Reporting Procedures for Disease-related Events

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after randomization through EOS/safety follow-up visit, or 30 days after the last administration of IP, whichever is later**, are reported on the Event CRF as disease related**.

Disease-related events assessed by the investigator to be more severe than expected and/or related to the investigational medicinal product(s)/study treatment/protocol-required therapies and determined to be serious must be recorded on the event CRF as serious adverse events. Additionally, the

investigator is required to report a fatal disease-related event on the Event CRF as a disease-related event.

9.2.2 Adverse Events

9.2.2.1 Reporting Procedures for Adverse Events That Do Not Meet Serious Criteria

Adverse events possibly related to study procedures, adverse device effects and serious adverse events are reported from signing of the ICF. All other adverse events are reported from the time of randomization. The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur **from signing of the ICF or from the time of** randomization through **the** EOS/safety follow-up, or 30 days after the last administration of IP, whichever is later, are reported using the event CRF. Only adverse events possibly related to study procedures are to be collected during screening.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity,
- Assessment of relatedness to IP, the AMD (or AI/pen), or other protocol-required therapies, and
- Action taken.

The adverse event grading scale used will be the CTCAE. The grading scale used in this study is described in Appendix A.

The investigator must assess whether the adverse event is possibly related to the IP, the AMD (or AI/pen), or other protocol-required therapies. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by the IP, the AMD (or AI/pen), or other protocol-required therapies?" **Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.**

The investigator must assess whether the adverse event is possibly related to any study-mandated activity (eg, administration of IP, protocol-required therapies, device[s] and/or procedure [including any screening procedure(s)]). This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity (eg, administration of investigational product, protocol-required therapies, device[s]), and/or procedure?" **Relatedness**

means that there are facts or reasons to support a relationship between investigational product and the event.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

The investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of informed consent through EOS/safety follow-up visit, or 30 days after the last administration of IP, whichever is later are recorded in the subject's medical record and are submitted to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the Event CRF.

The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure?"

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summar**ies**, **medical records,** or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

To comply with worldwide reporting regulations for serious adverse events, the treatment assignment of subjects who develop serious, unexpected, and related adverse events may be unblinded by Amgen before submission to regulatory authorities. Investigators will receive notification of related serious adverse events reports sent to regulatory authorities in accordance with local requirements.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and GCP.

The investigator is to notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

If the electronic data capture (EDC) system is unavailable to the site staff to report the serious adverse event, the information is to be reported to Amgen via an electronic Serious Adverse Event Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet /electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the Serious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

In addition to the attributes listed in Section 9.2.2.1, the investigator must also complete the serious adverse event section of the Event CRF.

9.2.2.3 Reporting Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after EOS. However, these serious adverse events can be reported to Amgen. In some countries (eg, European Union [EU] member states), investigators are required to report serious adverse events that they become aware of after EOS. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

9.2.2.4 Serious Adverse Events That are not to be Reported in an Expedited Manner

Hospitalizations due to chronic HIV complications are anticipated to possibly occur in the enrolled subject population.

The Amgen Safety Analysis team and medical team will review accumulating events on a regular basis.

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or a male **subject fathers a child,** while the subject is taking **evolocumab/placebo,** report the pregnancy to Amgen Global Patient Safety as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies through 15 weeks after the end of treatment with evolocumab/placebo.

The pregnancy should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant. If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly), the investigator will report the event as a serious adverse event.

If a lactation case occurs while the female subject is taking protocol-required therapies report the lactation case to Amgen **Global Patient Safety** as specified below.

In addition to reporting a lactation case during the study, investigators should **report** lactation cases that occur after the last dose of protocol-required therapies through 15 weeks after the end of treatment with evolocumab/placebo.

Any lactation case should be reported to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C). Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoints

10.1.1.1 Primary Endpoint

- Percent change from baseline in LDL-C at week 24

10.1.1.2 Secondary Endpoints

For week 24 the following secondary endpoints will be characterized:

- Tier 1
  - Change from baseline in LDL-C
  - Percent change from baseline in non-HDL-C
  - Percent change from baseline in ApoB
  - Percent change from baseline in TC
  - Achievement of target LDL-C <70 mg/dL (1.8 mmol/L)
  - LDL-C response (50% reduction of LDL-C from baseline)
- Tier 2
  - Percent change from baseline in Lp(a)
  - Percent change from baseline in triglycerides
  - Percent change from baseline in HDL-C
  - Percent change from baseline in VLDL-C

10.1.1.3 Safety Endpoints

- Subject incidence of treatment emergent adverse events
- Safety laboratory values and vital signs at each scheduled assessment
- Incidence of anti-evolocumab antibody (binding and neutralizing) formation

10.1.1.4 Exploratory Endpoints

10.1.2 Analysis Sets

10.1.2.1 Double-blind Treatment Period

The full analysis set (FAS) includes all randomized subjects who receive at least one dose of IP in the double-blind treatment period. This analysis set will be used in both efficacy and safety analyses. In efficacy analysis, subjects will be analyzed according to their randomized treatment group assignment. For safety analysis, subjects will be analyzed according to their randomized treatment group assignment except for the following case: if a subject receives a treatment that is different than the randomized treatment assignment throughout the study, then this subject will be analyzed by the treatment received.

The completer analysis set (CAS) includes subjects in the FAS who adhered to the scheduled IP regimen in the double-blind treatment period and have observed value for the primary endpoints.

10.1.2.2 Open-label Period

The long-term analysis set (LAS) will include all subjects who received at least 1 dose of open-label IP in the open-label period. This analysis set will be used in all analyses for the open-label period.

10.1.3 Covariates and Subgroups

[redacted] Baseline covariates include, but are not limited to:

- Stratification factors in Double-blind Treatment Period:
  - Statin use at baseline (yes/no)
  - Hepatitis C status (yes/no)
- Age: <65 year, ≥ 65 years
- Sex
- Race
- Study baseline LDL-C: <median/≥median
- Family history of premature coronary heart disease (yes/no)
- [redacted]

10.2 Sample Size Considerations

The planned sample size for the comparison between evolocumab 420 mg QM and placebo at a ratio of 2:1 in the double-blind treatment period is 450 total subjects.

The primary analysis will require the 2-sided tests of the primary endpoint to be significant at a level of 0.05. The planned sample size should provide adequate power to determine the superiority of evolocumab 420 mg QM relative to placebo as measured by the primary endpoint. From the integrated efficacy analysis of completed phase 3 studies, the treatment effect of evolocumab 420 mg QM compared to placebo and the corresponding 95% confidence interval at week 12 was -61.98% [-69.51%, -60.45%], with treatment effect ranges between -55.1% and -62.33% from Studies 20110114, 20110115, and 20110117. The assumed treatment effect between the primary endpoint in evolocumab 420 mg QM is 40%, with a common standard deviation (SD) of 20%. This SD assumption is based on evolocumab phase 3 results.

This sample size will provide approximately 99% power for the primary endpoint in testing the superiority of evolocumab dose regimen over placebo, assuming a dropout rate of 10%.

In addition, 300 subjects in evolocumab 420 mg QM group will provide approximately 95% probability of detecting adverse events that occur at a rate of 1%.

10.3 Access to Individual Subject Treatment Assignments by Amgen or Designees

Blinded individuals will not have access to unblinded information until the study is formally unblinded. Unblinding and potentially unblinding information should not be distributed to the study team, investigators or subjects prior to the study being formally unblinded (eg, the formal unblinding may occur at the final analysis rather than during the primary analysis) except as specified (eg, Section 5.2 and Section 9.2.2.2).

10.4 Planned Analyses

10.4.1 Primary Analysis

To evaluate efficacy and safety of 24 weeks of evolocumab 420 mg QM compared with placebo, the primary analysis will be performed when all randomized subjects in the double-blind treatment period have either completed all the scheduled study visits in the double-blind treatment period or have early terminated from the study. At that time, the database related to the primary analyses of the study will be cleaned, processed and a snapshot will be taken; the study will also be unblinded.

10.4.2 Final Analysis

The final analysis will be conducted when all subjects in the open-label period have either completed all the scheduled study visits in the open-label period or have early terminated from the study. At that time, the database will be cleaned, processed and a snapshot will be taken. The final analysis will be done to evaluate long-term safety and efficacy of evolocumab 420 mg QM.

10.5 Planned Methods of Analysis

10.5.1 General Considerations

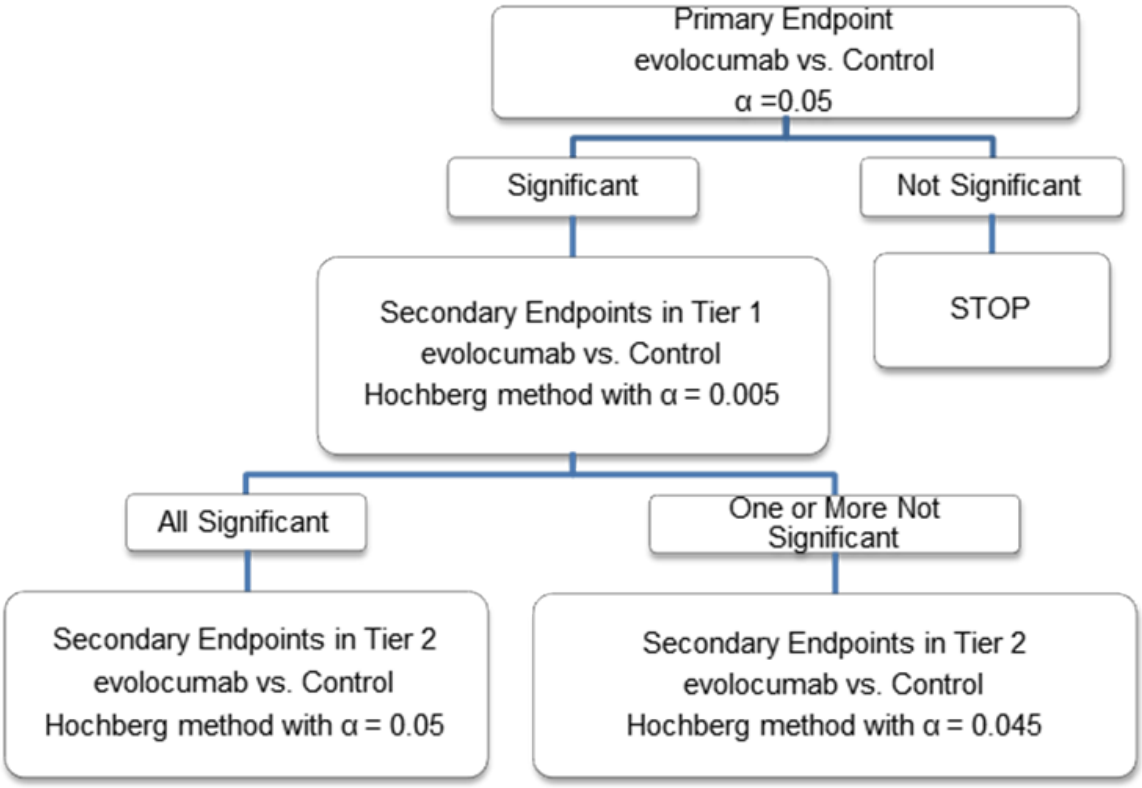
Based on the snapshot for the primary analysis, efficacy and safety analyses will be performed on FAS for the double-blind treatment period unless otherwise specified, and data will be summarized by randomized treatment group. Based on the snapshot for the final analysis, long-term efficacy and safety analyses will be performed on LAS and the analyses will be descriptive.

Subject disposition, demographics, baseline characteristics, and exposure to IP will be summarized by treatment group. Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, minimum, and maximum. For categorical variables, the frequency and percentage will be given. Methods of handling missing data for efficacy endpoints will be described below. Missing data will not be imputed for safety endpoints.

10.5.1.1 Multiplicity Adjustment Method

Methods of adjusting for multiplicity due to multiple endpoints (primary and secondary efficacy endpoints) in order to preserve the familywise error rate at 0.05 are described in Figure 1.

Figure 1. Multiplicity Adjustment Methods



The following method will be used to preserve the family-wise error rate for the primary and secondary endpoints:

1. If the treatment effect from the primary analysis of the primary endpoint is significant at a significance level of 0.05, statistical testing of the tier 1 secondary efficacy endpoints will follow the Hochberg procedure at a significance level of 0.005 (Hochberg, 1988)
2. If all tier 1 secondary efficacy endpoints are significant, the tier 2 secondary efficacy endpoints will be tested using the Hochberg procedure at a significance level of 0.05.
3. If not all tier 1 secondary efficacy endpoints are significant, the tier 2 secondary efficacy endpoints will be tested using the Hochberg procedure at a significance level of 0.045 (Wiens, 2003).

Unless specified otherwise, all other hypothesis testing will be 2-sided with a significance level of 0.05.

10.5.2 Primary Efficacy Endpoint

To assess the primary endpoint of the mean percent change from baseline in LDL-C at week 24, a repeated measures linear effects model will be used on the FAS to compare the efficacy of evolocumab with placebo. The repeated measures model will include terms for treatment group, stratification factors, scheduled visit and the interaction of treatment with scheduled visit. Missing values will not be imputed for primary analysis.

10.5.2.1 Sensitivity Analysis

To evaluate the robustness of the analysis results, sensitivity analyses will be performed as follows:

- The primary analysis will be repeated using the CAS
- Non-parametric analyses will be performed
- A sensitivity analysis under the assumption that subjects who discontinued IP with missing endpoint data have a mean zero percent change from baseline will be conducted.

Subgroup Analysis

If applicable, subgroup analyses on the primary endpoint will be conducted using the stratification factors or baseline covariates.

10.5.3 Secondary Efficacy Endpoints

The statistical model and testing of the tier 1 secondary efficacy endpoints will be similar to the primary analysis of primary endpoints. The secondary endpoint of LDL-C response (50% reduction of LDL-C from baseline and achievement of target LDL-C < 70 mg/d Las defined in secondary endpoint section) will be analyzed using the Cochran-Mantel Haenszel test adjusted by the stratification factors.

Analysis of the tier 2 secondary efficacy endpoints will use the same analysis model as the tier 1 endpoints.

Multiplicity adjustment procedures are defined in Section 10.5.1.1.

10.5.4 Safety Endpoints

The current Medical Dictionary for Regulatory Activities version at the time of the data lock will be used to code all adverse events to a system organ class and a preferred term.

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from IP, device-related adverse events, and

significant treatment-emergent adverse events will also be provided. Subject-level data may be provided instead of tables if the subject incidence is low.

Subject incidence of all disease-related events and fatal disease-related events will be tabulated by system organ class and preferred term.

10.5.5 Exploratory Endpoints

[redacted]

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample ICF is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Clinical Study Manager to the investigator. The written informed consent document is to be prepared in the language(s) of the potential subject population. Amgen will require a copy of the site's IRB/IEC informed consent.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any IP is administered.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the ICF is to be signed and personally dated by the subject and by the person who conducted the informed consent discussion. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the

ICF to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the ICF to attest that informed consent was freely given and understood.

11.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed ICF, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written approval of the protocol and ICF must be received by Amgen before recruitment of subjects into the study and shipment of Amgen IP.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual IRB/IEC approval renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.
- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed ICFs) are to be kept in confidence by the investigator, except as described below.

In compliance with ICH Tripartite Guideline on GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that

are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An Investigator who provided significant contributions to either the design or interpretation of the study
- An investigator contributing a high number of eligible subjects

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the investigator must be obtained. The IRB/IEC must be informed of all amendments and give approval. The investigator must send a copy of the approval letter from the IRB/IEC to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the investigator reserve the right to terminate the investigator's participation in the study according to the study contract. The investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen IP by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen IP and by what mechanism, after termination of the study and before the product(s) is/are available commercially.

12.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

In this study, the IVRS/IWRS system captures the following data points and these are considered source data:

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, ICFs, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- Investigational product-related correspondence including Proof of Receipts, IP Accountability Record(s), Return of IP for Destruction Form(s), Final IP Reconciliation Statement, as applicable.

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen Clinical Monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

The investigator agrees to cooperate with the Clinical Monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage

areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the CRFs must be maintained and readily available.
- Updates to CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries are created in the EDC system database for site resolution and subsequently closed by the EDC system or by an Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study or the investigator applies an electronic signature in the EDC system if the study is set up to accept an electronic signature. This signature indicates that investigator inspected or reviewed the data on the CRF, the data queries, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit-week 4 and early termination) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 3), the investigator can search publically available records [where permitted] to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.6 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the ICF that is available as a separate document.

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14. APPENDICES

Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

Refer to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. The CTCAE is available at the following link:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL according to the criteria specified in Section 6.3 require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section 9.2.2.2.

Additional Clinical Assessments and Observation

All subjects in whom IP or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Sections 6.3.1 and 6.3.2 or are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Assessments that are to be performed during this period include:

- AST, ALT, ALP, and bilirubin (total and direct) is to be repeated within 24 hours
- In cases of TBL > 2x ULN, retesting of liver tests, and bilirubin (total and direct) is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the IP or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

- Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL:
  - Obtain complete blood count with differential to assess for eosinophilia
  - Obtain serum total immunoglobulin IgG, Anti-nuclear antibody (ANA), Anti Smooth Muscle Antibody, and Liver Kidney Microsomal antibody 1 (LKM1) to assess for autoimmune hepatitis
  - Obtain serum acetaminophen (paracetamol) levels
  - Obtain a more detailed history of:
    - Prior and/or concurrent diseases or illness
    - Exposure to environmental and/or industrial chemical agents
    - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting, and fever
    - Prior and/or concurrent use of alcohol, recreational drugs and special diets
    - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
  - Obtain viral serologies
  - Obtain CPK, haptoglobin, lactate dehydrogenase, and peripheral blood smear
  - Perform appropriate liver imaging if clinically indicated
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Obtain hepatology consult (liver biopsy may be considered in consultation with an hepatologist)
- Follow the subject and the laboratory tests (ALT, AST, and TBL) until all laboratory abnormalities return to baseline or normal. The “close observation period” is to continue for a minimum of 4 weeks after discontinuation of all IP and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in corresponding CRFs.

Appendix B. Sample eSerious Adverse Event Contingency Report Form

A **Study # 20130286** Evolocumab (AMG 145)	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<< For completion by COM prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____

and start date: Day _____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____Month___Year____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	Is event a potential endpoint?	If serious, enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that the Event may have been caused by IP or an Amgen device used to administer the IP? Evolocumab (AMG145) No / Yes; Prefilled Autoinjector Pen (Aipen) No / Yes; Automated Mini-Doser (AMD)	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No	☐Yes ☐No				
				☐Yes ☐No	☐Yes ☐No				
				☐Yes ☐No	☐Yes ☐No				

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required/prolonged hospitalization; **04** Persistent or significant disability / incapacity; **05** Congenital anomaly / birth defect; **06** Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

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A **Study # 20130286** Evolocumab (AMG 145)	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
Evolocumab (AMG 145)	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Prefilled Autoinjector/Pen (AI/Pen) - *Amgen device*	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
Automated Mini-Doser (AMD) - *Amgen device*	☒ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	 Yes✓	Continuing No✓	 Yes✓	Dose	Route	Freq.	Treatment Med No✓	 Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Test											
	Unit											

A **Study # 20130286** Evolocumab (AMG 145)	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

	Site Number	Subject ID Number	

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Additional Tests	Results	Units

10. CASE DESCRIPTION *(Provide narrative details of events listed in section 3)* Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - _____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

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Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: 20130286

Study Design: ■ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm /dd /yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm / dd / yyyy_____ ☐ Unknown

Estimated date of delivery mm / dd / yyyy_____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm / dd / yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm / dd / yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: March 27, 2011

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AMGEN Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# enter fax number

1. Case Administrative Information

Protocol/Study Number: 20130286

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

Amendment 1

Protocol Title: A Double Blind, Randomized, Placebo Controlled, Multicenter Study to Evaluate Safety, Tolerability, and Efficacy on LDL-C of Evolocumab (AMG 145) in Subjects With HIV and With Hyperlipidemia and/or Mixed Dyslipidemia

Amgen Protocol Number EVO 20130286

BEIJERINCK: evolocuma<u>B</u> <u>E</u>ffect on LDL-C lower<u>I</u>ng in sub<u>JE</u>cts with human immunodeficiency vi<u>R</u>us and <u>IN</u>creased <u>C</u>ardiovascular ris<u>K</u>

Amendment Date: 30 January 2017

Rationale:

Regulatory agencies had expressed concerns that HIV-positive subjects without clinical atherosclerotic cardiovascular disease (ASCVD) with LDL ≥ 70 mg/dL but ≤ 100 mg/dL would be eligible to this study. The protocol was amended to address the regulators' concerns. Per this amendment, subjects with clinical ASCVD disease with LDL ≥ 70 mg/dL are eligible for this study. For subjects without clinical ASCVD, LDL must be ≥ 100 mg/dL.

Additionally, regulators suggested that a subpopulation of subjects not on statin background therapy be included in this study. They also inquired about a prespecified size for that subpopulation that would allow for generalizability of the study results. Feasibility analysis suggest that such a population is very small in clinical practice. For this study, per amendment, we will aim to enroll a subpopulation of subjects needing lipid-lowering therapy but not on statin therapy, congruent with the reality of clinical practice. We anticipate this subpopulation not on statin therapy to be about 10%. In the protocol, a size for this subpopulation is not prespecified, but text was added regarding stratification of randomization by statin treatment to include the expected percentage of subjects on statin treatment. The European Medicines Agency did not mandate a cap or subgroup size.

This amendment also clarifies the definition of statin intolerance in inclusion criterion 106.

Sections of the protocol concerning temporary withholding and permanent discontinuation of investigational product in response to hepatotoxicity, pregnancy and

lactation reporting, and disease-related event reporting were updated to reflect current Amgen guidelines. The electronic Serious Adverse Event Contingency form (Appendix B) was replaced with the current version of the form.

Further, to address how HIV worsening will be classified, a section was added to clarify that HIV worsening will be recorded as an adverse event. In the case of HIV worsening, because of potential drug–drug interaction between statins and antiretroviral therapy, changing background lipid-lowering therapy is left to the judgment of the investigator.

In addition to these changes, the pregnancy test schedule was revised to address regulatory agency concerns, and details were provided to clarify when serum and urine pregnancy tests will be performed.

Minor administrative and typographical changes were made throughout the protocol.

Description of Changes:

Section: Global

Change: Minor corrections throughout (eg, typographical, punctuation, and spelling errors; revision of dates); administrative changes on page 1 (added short title of protocol; updated name and added contact information for Global Clinical Trial Manager); addition of terms to Study Glossary.

Section: Synopsis

Summary of Subject Eligibility Criteria

Replace:

The study will enroll adult subjects (≥ 18 years of age) with known HIV infection, on maximally tolerated statin therapy (maximally tolerated statin can include no type or dose of statin in those diagnosed as statin intolerant) who have received HIV therapy that has been stable for ≥ 6 months prior to randomization and that is not expected to change during the duration of study participation, and who have fasting LDL-C of ≥ 70 mg/dL (1.8 mmol/L) or non-HDL-C ≥ 100 mg/dL (2.6 mmol/L) and fasting triglycerides ≤ 600 mg/dL (6.8 mmol/L). Subjects who are receiving lipid-lowering therapy must have been on a stable dose for ≥ 4 weeks prior to randomization.

With:

The study will enroll adult subjects (≥ 18 years of age) with known HIV infection, **who have received stable HIV therapy for ≥ 6 months prior to randomization and that is not expected to change during the duration of study participation. Subjects must be on stable doses of lipid-lowering therapy for ≥ 4 weeks prior to randomization and not expected to change during the duration of study participation. Subjects should be on maximally tolerated dose of statins. For some subjects, "maximally tolerated" may indicate no statin at all due to statin intolerance or contraindication to statin therapy. A statin-intolerant subject must meet the criteria described in Section 4.1.1, criterion 106. Statin intolerance or contraindication must be documented. Subjects without known clinical atherosclerotic CVD (ASCVD) must have fasting LDL-C of ≥ 100 mg/dL (2.6 mmol/L) or non-HDL-C of ≥ 130 mg/dL (3.4 mmol/L) as determined by the central laboratory at screening. Subjects with known clinical ASCVD must have fasting LDL-C of ≥ 70 mg/dL (1.8 mmol/L) or non-HDL-C of ≥ 100mg/dL (2.6 mmol/L) as determined by the central laboratory.**

Clinical ASCVD is defined as a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin. Subjects must also have fasting triglycerides ≤ 600 mg/dL (6.8 mmol/L).

Amgen Investigational Product

Replace:

The Amgen investigational product (IP) is the IMP plus the device (AMD or AI/pen).

With:

The Amgen investigational product (IP) is the IMP plus the device (AMD **[called an "on-body infuser prefilled cartridge" in the United States]** or AI/pen).

Double-blind Treatment Period

Replace:

The IP is expected to be delivered by AMD but may be achieved by 3 injections with AI/pen if AMD not available.

With:

The IP **may** be delivered by AMD **or by** 3 injections with AI/pen.

Procedures:

First paragraph

Replace:

Subjects will undergo SC placebo injection with device to be used during study (AMD, or AI/Pen) during screening.

With:

Subjects will undergo SC placebo injection with **the** device **anticipated** to be used during study (AMD or AI/pen) during screening.

Second and third paragraphs

Replace:

Laboratory tests will be conducted at day 1 (fasting lipids, apolipoprotein A-1 (ApoA1), ApoB, Lp(a), [redacted]

[redacted] HIV viral load and cluster of differentiation 4 (CD4), hepatitis C virus (HCV) viral load, (if applicable) chemistry, urinalysis, hematology HbA1c biomarkers [blood], and anti-evolocumab antibodies) and week 12 (fasting lipids, ApoA1, ApoB, Lp(a), [redacted], HIV viral load and CD4, HCV viral load, [if applicable] chemistry, urinalysis, hematology, HbA1c, biomarkers [blood], and anti-evolocumab antibodies). Vital signs, safety data reporting, and concomitant therapy will be recorded at each visit. At the end of the double-blind treatment period at week 24, laboratory tests (fasting lipids, ApoA1, ApoB, Lp(a),[redacted], HIV viral load and CD4, HCV viral load, [if applicable] chemistry, urinalysis, hematology, serum pregnancy [follicle-stimulating hormone/luteinizing hormone (FSH/LH)/estradiol] [if applicable], hemoglobin A1c (HbA1c), biomarkers [blood], and anti-evolocumab antibodies) will be conducted and vital signs, safety data reporting, concomitant therapy, physical examination, and body weight/waist circumference will be recorded.

Following the double-blind treatment period, subjects who received a dose of IP at week 20 will continue to a 52-week open-label period in which all subjects will be treated with QM evolocumab at weeks 28, 32, 36, 40, 44, and 48. Laboratory tests will be conducted at week 36 (fasting lipids, ApoA1, ApoB, Lp(a), [redacted], HIV viral load and CD4, HCV viral load [if applicable] chemistry, urinalysis, hematology, HbA1c, and anti-evolocumab antibodies) and week 52 (fasting lipids, ApoA1, ApoB, Lp(a), [redacted], HIV viral load and CD4, HCV viral load, (if applicable) chemistry, urinalysis, hematology, serum pregnancy [FSH/LH/estradiol] [if applicable], HbA1c, biomarkers [blood], and anti-evolocumab antibodies). Vital signs, safety data reporting, and concomitant therapy will be recorded at week 36. At end of study week 52, vital signs, safety data reporting, concomitant therapy, physical examination, body weight, and waist circumference will be recorded.

With:

Laboratory tests will be conducted at day 1 and week 12. Vital signs, safety data reporting, **urine pregnancy testing (as applicable),** and concomitant therapy will be recorded at each visit. At the end of the double-blind treatment period at week 24, laboratory tests will be conducted, and vital signs, safety data reporting, **urine pregnancy testing (as applicable)** concomitant therapy, physical examination, and body weight/waist circumference will be recorded.

Following the double-blind treatment period, subjects who received a dose of IP at week 20 will continue to a **24**-week open-label period in which all subjects will be treated

with QM evolocumab at weeks **24,** 28, 32, 36, 40, 44, and 48. Laboratory tests will be conducted at week 36 and week 52. Vital signs, safety data reporting, **urine pregnancy testing (as applicable),** and concomitant therapy will be recorded at week 36. At end of study week 52, vital signs, safety data reporting, **urine pregnancy testing (as applicable),** concomitant therapy, physical examination, body weight, and waist circumference will be recorded.

Section: 2.3, Rationale

Replace:

It is anticipated that evolocumab may be used in HIV-infected individuals who cannot achieve optimal LDL-C despite the use of maximally tolerated statin therapy or who are intolerant to statin.

With:

It is anticipated that evolocumab may be used in HIV-infected individuals who cannot achieve optimal LDL-C despite the use of maximally tolerated statin therapy or who are intolerant to statin **or for whom statin is contraindicated.**

Section: 3.1, Study Design

Replace:

Randomization will be stratified by entry statin treatment (yes/no**)** and hepatitis C status (yes/no).

The double-blind treatment period will be 24 weeks, after which subjects who received a dose of investigational product (IP) at week 20 will continue in an open-label period during which all subjects will be treated with QM evolocumab.

With:

Randomization will be stratified by entry statin treatment (yes/no) and by hepatitis C status (yes/no). **The size of the subgroup not on statin therapy is expected to be approximately 10% and no more than 20% of the subjects. This enrollment projection is expected to be reflective of clinical practice.**

The double-blind period will be 24 weeks, after which subjects who received a dose of investigational product (IP) at week 20 will continue in an open-label period during which all subjects will be treated with QM evolocumab.

Last paragraph

Replace:

SC evolocumab and placebo will be administered QM at the study site or appropriate non-investigator site settings (eg, at the subject's home) by automated mini-doser (AMD) or by spring-based prefilled autoinjector/pen (AI/Pen) if AMD is not available.

With:

SC evolocumab and placebo will be administered QM at the study site or appropriate non-investigator site settings (eg, at the subject's home) by automated mini-doser (AMD**; referred to in the United States as an "on-body infuser prefilled cartridge"**) or by spring-based prefilled autoinjector/pen (AI/pen).

Section: 3.2 Number of Sites

Replace:

Approximately 70 sites globally will participate in this study.

With:

Approximately **75** sites globally will participate in this study.

Section: 4.1.1 Inclusion Criteria

Replace:

106 Subject on stable dose of maximally tolerated statin therapy for ≥ 4 weeks prior to randomization. For subjects whose maximally tolerated dose of statin is no type or dose (ie, determined to be statin intolerant by primary investigator), background lipid-lowering therapy is not required

With:

101 106 Subject on stable **lipid-lowering therapy** for ≥ 4 weeks prior to randomization **and not expected to change during the duration of study participation**. **Subjects should be on** maximally tolerated dose of statin**s. For some subjects, "maximally tolerated" may indicate no statin at all due to statin intolerance or contraindication to statin therapy. Statin intolerance or contraindication must be documented. A subject with statin intolerance must be evidenced by the following:**

a. Must have tried at least 2 statins with failure to at least 1 of the statins at an average daily dose at or below the following doses due to intolerable myopathy (ie, myalgia [muscle pain, ache, or weakness without creatine kinase elevation]), myositis (muscle symptoms with increased creatine kinase levels), or rhabdomyolysis (muscle symptoms with marked creatine elevation, as defined under "b"):

- **atorvastatin: 10 mg**
- **simvastatin: 10 mg**
- **pravastatin: 40 mg**
- **rosuvastatin: 5 mg**
- **lovastatin: 20 mg**
- **fluvastatin: 40 mg**
- **pitavastatin: 2 mg**

AND

b. Symptoms resolved or improved when statin dose was decreased or discontinued

For subjects that developed rhabdomyolysis, defined as creatine kinase > 10 × upper limit of normal (ULN), failure of only 1 statin at any dose is acceptable.

Replace:

107 Fasting LDL-C of ≥ 70 mg/dL (1.8 mmol/L) or non-HDL-C ≥ 100 mg/dL (2.6 mmol/L) as determined by central laboratory during screening

With:

107 **Subject without known clinical atherosclerotic CVD (ASCVD): fasting LDL-C of ≥ 100 mg/dL (2.6 mmol/L) or non-HDL-C of ≥ 130 mg/dL (3.4 mmol/L) as determined by the central laboratory at screening. Subject with known clinical ASCVD:** fasting LDL-C of ≥ 70 mg/dL (1.8 mmol/L) or non-HDL-C of ≥ 100 mg/dL (2.6 mmol/L) as determined by the central laboratory. **Clinical ASCVD is defined as a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin.**

Section: 5 Subject Enrollment

Replace:

Subjects who are unable to complete or meet eligibility on initial screening will be permitted to re-screen except for subjects with LDL-C <70 mg/dL and non-HDL-C < 100 mg/dL by central lab result during screening (see Section 7.2.2).

With:

Subjects who are unable to complete or meet eligibility on initial screening will be permitted to re-screen, except for subjects **who do not meet inclusion criterion 107** (see Section 7.2.2).

Section: 5.1 Randomization/Treatment Assignment

Last paragraph

Replace:

The randomization date is to be documented in the subject's medical record and on the enrollment CRF.

With:

The randomization date **(study day 1)** is to be documented in the subject's medical record and on the enrollment CRF.

Section: 6.1 Classification of Product(s) or Medical Devices(s)

Second paragraph

Replace:

The investigational medical device is the AMD, or the spring based prefilled AI/Pen if AMD is not available.

With:

The investigational medical device is the AMD, or the spring based prefilled AI/pen.

Section: 6.2.1.2 Double-blind Treatment Period

Second paragraph, add:

See Table 3 for the schedule of in-clinic visits.

Section: 6.2.1.3 Open-label Period

Replace:

Dosing at week 24 is expected to be in-clinic while dosing for weeks 28, 32, 36, 40, 44, and 48 is expected to be in an appropriate non-clinic setting (eg, at the subject's home). Subjects who do not wish to self-inject at home may return to the clinic for injection.

With:

Dosing at week 24 is expected to be in-clinic while dosing for weeks 28, 32, 36, 40, 44, and 48 is expected to be in an appropriate non-clinic setting (eg, at the subject's home, **even on weeks with in-clinic visits**); **however,** subjects who do not wish to self-inject at home may return to the clinic for injection.

Section: 6.3 Hepatotoxicity Stopping and Rechallenge Rules

Replace:

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], AST, ALT, total bilirubin [TBL]) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen IP or other protocol-required therapies as specified in the Guidance for Industry Drug-Induced Liver Injury (DILI): Premarketing Clinical Evaluation (July 2009).

With:

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], AST, ALT, total bilirubin [TBL]) **and/or international normalized ratio (INR)** and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen IP or other protocol-required therapies as specified in the Guidance for Industry Drug-Induced Liver Injury (DILI): Premarketing Clinical Evaluation (July 2009).

Section: 6.3.1 Criteria for Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Delete

- TBL ≥ 2x ULN
- AND increased AST or ALT ≥ 3x ULN from a baseline value were less than the ULN
- AND ALP < 2x ULN
- AND no other cause for the combination of the above laboratory abnormalities is immediately apparent; important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

Add:

6.3.1 Criteria for **Withholding or** Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules (Table 1) apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

Table 1. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
Total bilirubin	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5 (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or total bilirubin values > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x ULN at any time	--

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; ULN=upper limit of normal.

Move from original Section 6.3.3 to Section 6.3.1:

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.3.2).

Section: 6.3.2 Criteria for Conditional Withholding of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

Delete entire section

Section: 6.7 Product Complaints

Replace:

A product complaint is defined by Amgen as any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability,

reliability, safety, effectiveness, or performance of a drug(s) or device(s**)** after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

With:

A product complaint is defined by Amgen as any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s)**,** device(s**), or combination products** after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

Section: 6.8 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

Add:

- any lipid-lowering therapies not taken at the time of screening and enrollment **(unless required in response to HIV worsening; see Section 9.1.2.1)**.

Section: 7 Study Procedures

Replace:

All on-study visits and dosing should be scheduled from day 1 (first IP administration).

With:

All on-study visits and dosing should be scheduled from day 1 (**randomization and** first IP administration).

Section: 7.1 Table **3** Schedule of Assessments

Table body

Add:

Hepatitis C viral load assessment **at screening**

Urine pregnancy[e] test at Day 1, Weeks 12, 20, 24**, and 36**

IP administration **(every 4 weeks)**; **Week 12** and **Week 36** timepoints added

Footnote **a** to column header “Week 24 ± 3 days”; re-letter remaining footnotes in table

Footnote **a: At week 24, final double-blind period assessments will be conducted, and the first dose of open-label study drug will be administered.**

Footnote b

Replace:

Including review for adverse events/serious adverse events/disease-related events/adverse device effects. Only adverse events/adverse device effects possibly related to study procedures, and serious adverse events are collected during the screening from signing of the informed consent.

With:

Including review for adverse events/serious adverse events/disease-related events/adverse device effects. **Adverse events possibly related to study procedures, adverse device effects and serious adverse events are reported from signing of the informed consent form. All other adverse events are reported from the time of randomization.**

Footnote e

Add:

Serum pregnancy testing at screening. Urine pregnancy testing at day 1 and weeks 12, 20, 24, 36, and prior to IP administration and at EOS.

Footnote f

Replace:

FSH/LH/estradiol only at screening if applicable.

With:

FSH/LH/estradiol only at screening **for menopausal women**.

Footnote g

Replace:

During the double-blind treatment period, in addition to the in-clinic administration at day 1 and week 20,

With:

During the double-blind period, in addition to the in-clinic administration at day 1 and week 20,

Section: 7.2.2 Rescreening

Replace:

Subjects with LDL-C <70 mg/dL and non-HDL-C < 100 mg/dL by central lab result during screening are considered screen failures and cannot be rescreened for this study.

With:

Subjects **who do not meet inclusion criterion 107** are considered screen failures and cannot be rescreened for this study.

Section: 7.2.3 Double-blind Treatment Period

Replace:

Visits will occur per the Schedule of Assessments (Table 2) during the treatment period from day 1 (week 1, baseline) through week 24.

With:

Visits will occur per the Schedule of Assessments (Table **3**) during the **double-blind** period from day 1 (week 1, baseline) through week 24.

Section: 7.2.4 Open-label Period

Replace:

Subjects who receive a dose of IP at week 20 will continue in an open-label period. Visits will occur per the Schedule of Assessments (Table 2) at weeks 36 and 52. Visits during the open-label period must be completed within ± 7 days of the target visit date.

With:

Subjects who receive a dose of IP at week 20 will continue in an open-label period. **They will receive their first dose of open-label IP at the week 24 visit.** Visits will **then** occur per the Schedule of Assessments (Table **3**) at weeks 36 and 52. Visits during the open-label period must be completed within ± 7 days of the target visit date.

Section: 7.2.5 End of Study / Safety Follow-up

Add:

At week 52 or 30 days after the last administration of IP, whichever is later, a safety follow-up is scheduled to occur. This safety follow-up can be an in-person visit to the study center or another contact with the subject. **If the end-of-study visit is < 30 days**

after the last dose of IP, the subject will be contacted (eg, by phone) at 30 (± 7 days) after last IP for safety follow-up.

Section: 7.3.4 Vital Signs

Replace:

The position should be the same that is used throughout the study and documented on the vital sign CRF.

With:

The **same arm and same** position should be used throughout the study and documented on the vital sign CRF.

Section: 7.3.5 Safety Data Reporting

Replace:

Adverse events, serious adverse events, disease-related events, and adverse device effects observed by the investigator or reported by the subject will be collected at all study visits from the signing of the informed consent through EOS as detailed in Section 9. Only adverse events or adverse device effects possibly related to study procedures and serious adverse events are collected during screening.

With:

Adverse events, serious adverse events, disease-related events, and adverse device effects observed by the investigator or reported by the subject will be collected at all study visits from **randomization** through EOS as detailed in Section 9. Adverse events **possibly related to study procedures,** adverse device effects and serious adverse events are collected during screening.

Section: 7.4 Laboratory Assessments

Replace:

All laboratory samples will be sent to the central laboratory.

Specific analytes for serum chemistry, coagulation, urinalysis, hematology, and other labs to be conducted on blood and urine samples are shown in Table 3.

With:

All laboratory samples will be sent to the central laboratory**, except for samples for urine pregnancy tests, which will be conducted by the local laboratory**.

Specific analytes for serum chemistry, urinalysis, hematology, and other labs to be conducted on blood and urine samples are shown in Table **4**.

Section : Table **4** Analyte Listing

Delete: Coagulation (column heading)

PT/INR (table text)

Add:

Urine pregnancy test (females of childbearing potential) in Urinalysis column

Section: 7.4.2 Serum Pregnancy Test

Replace:

All females, except those who are confirmed surgically sterile or at least 2 years postmenopausal or 1 year postmenopausal if ≥ 55 years old, must have a negative serum pregnancy test at baseline, prior to administering the first dose of evolocumab/placebo. The central laboratory will provide the baseline pregnancy tests.

With:

Section: 7.4.2 Pregnancy Test**s**

All females, except those who are confirmed surgically sterile or at least 2 years postmenopausal or 1 year postmenopausal if ≥ 55 years old, must have a negative serum pregnancy test at **screening**, prior to administering the first dose of evolocumab/placebo. The central laboratory will provide the **screening** pregnancy tests.

Urine pregnancy tests will be performed on day 1 and on weeks 12, 20, 24, and 36 before IP administration and at EOS.

Section: 9.1.1 Disease-related Events

Replace:

Disease-related events and/or disease related outcomes that do not qualify as serious adverse events:

With:

Disease-related events and/or disease related outcomes that do not qualify as **adverse events or** serious adverse events:

Replace:

If the outcome of the underlying disease is worse than that which would normally be expected for the subject, or if the investigator believes there is a causal relationship between the IP/study treatment protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event.

With:

A disease-related event that would qualify as an adverse event or serious adverse event is an event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition or an event for which the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol required therapies and disease worsening. This must be reported as an adverse event or serious adverse event.

Section: 9.1.2 Adverse Events

Add:

Section 9.1.2.1, Worsening of HIV Disease

HIV worsening will be captured as an adverse event. Because evolocumab is not expected to have any interaction with antiretroviral therapy or viral load or consequences of HIV infection, no specific actions with respect to study participation (including investigational product) are expected of the investigator. Should a subject's viral load change or HIV infection worsen, the investigator is expected to manage HIV infection or any other concomitant illnesses per his or her clinical judgment. Background lipid-lowering therapy is expected to be stable. However, in the case of HIV worsening, because of potential drug–drug interaction between statins and antiretroviral therapy, changing background lipid-lowering therapy is left to the judgment of the investigator.

Section: 9.2.1 Reporting Procedures for Disease-related Events

Replace:

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after randomization through EOS/safety follow-up visit, or 30 days after the last administration of IP, whichever is later. Disease-related events are reported using the Event CRF, and additionally, the investigator is required to report a fatal Disease Related Event on the Event CRF.

Events assessed by the investigator to be serious, require reporting of the event on the Event CRF.

Events assessed by the investigator to be related to the investigational medicinal product(s)/study treatment/protocol-required therapies, and determined to be serious, require reporting of the event on the Event CRF.

Events assessed by the investigator to be related to the IP/protocol-required therapies, and determined to be serious, require reporting of the event on the Event CRF.

With:

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after randomization through EOS/safety follow-up visit, or 30 days after the last administration of IP, whichever is later **are reported on the Event CRF as disease related**.

Disease-related events assessed by the investigator to be more severe than expected and/or related to the investigational medicinal product(s)/study treatment/protocol-required therapies and determined to be serious must be recorded on the event CRF as serious adverse events. Additionally, the investigator is required to report a fatal disease-related event on the Event CRF as a disease-related event.

Section: 9.2.2.1 Reporting Procedures for Adverse Events That Do Not Meet Serious Criteria

First paragraph, add:

Adverse events possibly related to study procedures, adverse device effects and serious adverse events are reported from signing of the ICF. All other adverse events are reported from the time of randomization.

Replace:

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after randomization through EOS/safety follow-up, or 30 days after the last administration of IP, whichever is later, are reported using the Event CRF.

With:

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur **from signing of the ICF or from the time of** randomization through **the** EOS/safety follow-up, or 30 days after the last administration of IP, whichever is later, are reported using the event CRF.

Fourth and fifth paragraphs, add last sentence:

Relatedness means that there are facts or reasons to support a relationship between investigational product and the event.

Section: 9.2.2.2 Reporting Procedures for Serious Adverse Events

Third paragraph, replace:

The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

With:

The investigator may be asked to provide additional follow-up information, which may include a discharge summar**ies**, **medical records,** or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

Section: 9.3 Pregnancy and Lactation Reporting

Replace:

If a pregnancy occurs in a female subject, or female partner of a male **subject,** while the subject is taking protocol-required **therapies** report the pregnancy to Amgen as specified below.

With:

If a pregnancy occurs in a female subject, or a male **subject fathers a child,** while the subject is taking **evolocumab/placebo,** report the pregnancy to Amgen Global Patient Safety as specified below.

Add fourth paragraph:

If a female subject becomes pregnant during the study, the investigator should attempt to obtain information regarding the birth outcome and health of the infant. If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly), the investigator will report the event as a serious adverse event.

Sixth paragraph, replace:

In addition to reporting a lactation case during the study, investigators should monitor lactation cases that occur after the last dose of protocol-required therapies through 15 weeks after the end of treatment with evolocumab/placebo.

With:

In addition to reporting a lactation case during the study, investigators should **report** lactation cases that occur after the last dose of protocol-required therapies through 15 weeks after the end of treatment with evolocumab/placebo.

Add eighth paragraph:

If a male subject's female partner becomes pregnant, the investigator should discuss obtaining information regarding the birth outcome and health of the infant from the pregnant partner.

Section: 10.1.3 Covariates and Subgroups

Add:

[redacted]

Section: Appendix B, Sample **e**Serious Adverse Event **Contingency** Report Form

Replaced form with current version